Synthetic approaches to the herbicidins

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SYNTHETIC APPROACHES TO THE HERBICIDINS

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To my parents for their

encouragement and support

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SUMMARY

Chapter 1 introduces the herbicidin group of natural products and our proposed synthetic strategy for their synthesis. This is followed by a review of the methods currently available for introducing carbon-carbon bonds at the "anomeric" or C(2) centre of pyranose rings.

Two related methods have been developed for the regiospecific introduction of a carbon-carbon bond to the C(2) centre of tetrahydropyran-3-one:

(i) The first involves the metalation of the enol ether (35)*, followed by reaction of the lithiated species (41)* with an electrophile. When the electrophile is an alkyl halide the carbonyl functionality can be deprotected with iodotrimethylsilane. This methodology has been used to synthesize the novel pyrano-pyran (29)* which contains the *C*-pyranoside linkage and the hemiketal function which are both present in the herbicidins.

(ii) The second method utilises the Lewis acid mediated reactions of the silyl enol ether (9)* with aldehydes and α-chlorosulphides. This chemistry has been used to synthesize a number of furo-pyrano-pyrans, e.g. (86a)* and (86b)*, species which contain a large proportion of the functionality and stereochemistry present in the herbicidins (see Scheme 22)*.

It is hoped that these methodologies can be extrapolated to the synthesis of the herbicidins and analogues thereof. Preliminary results presented, indicate that the second approach (silyl enol ether) is the most suitable.

* Numbers refer to Chapter 2 (Results and Discussion).

ABBREVIATIONS

The following abbreviations are used in the text;

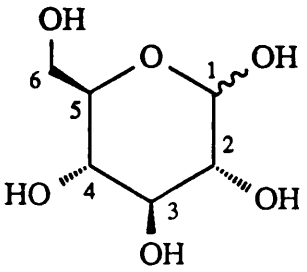
AB_q	AB quartet
Ac	acetyl
AIBN	azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
*t*BDMS	*tert*-butyldimethylsilyl
Bn	benzyl
b.p.	boiling point
br	broad
Bu	butyl
cat	catalyst
cf.	compare
conc.	concentrated
*m*CPBA	*meta*-chloroperoxybenzoic acid
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DET	diethyl tartate
DIBAL	diisobutylaluminium hydride
DIPHOS	diphosphine ligand
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
E^+	electrophile
equiv	equivalent
Et	ethyl
h	hours

Im	imidazole
i.r.	infra red
Iso-but	isobutane
J	coupling constant
LDA	lithium diisopropylamide
LDMAN	lithium-1-(dimethylamino)naphthalenide
LN	lithium napthalenide
LUMO	lowest unoccupied molecular orbital
M	molar
M^+	molecular ion
Me	methyl
MHz	megahertz
min	minutes
m.p.	melting point
MS	mass spectrum
MsCl	methanesulphonyl chloride
N	normal
n	straight chain
NCS	*N*-chlorosuccinamide
n.m.r.	nuclear magnetic resonance
n.O.e.	nuclear Overhauser effect
Nu	nucleohile
p	para
Ph	phenyl
PNB	*para*-nitrobenzyl
Py	pyridine
ref	reference
R_f	retention factor

r.t.	room temperature
s	singlet
s	secondary
SOMO	singly occupied molecular orbital
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TCAI	trichloroacetimidate
tert (*t*)	tertiary
Tf	trifluoromethanesulphonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
t.l.c.	thin layer chromatography
TMS	trimethylsilane — tetramethylsilane ?
Tos	*para*-toluenesulphonyl
u.v.	ultra violet
w	weak
Δ	heat
δ	chemical shift

NUMBERING CONVENTIONS

Two numbering systems are commonly used in the literature with regard to pyranose rings. The first, derives from carbohydrate nomenclature and labels the anomeric centre 1, e.g. structure 1. The second numbering system derives from



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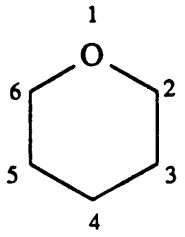
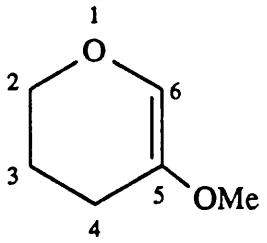


2

tetrahydropyran nomenclature where the ring oxygen is labelled 1 as in structure 2. To simplify the ensueing discussion the second convention (i.e. structure 2) has been used throughout when referring to either simple or substituted pyrans.

Other numbering systems used in this thesis are illustrated below.



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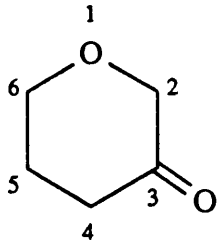

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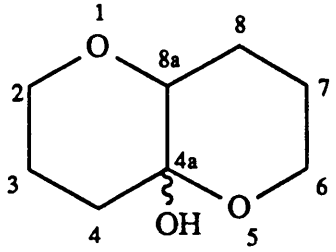

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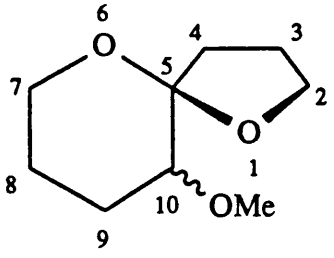

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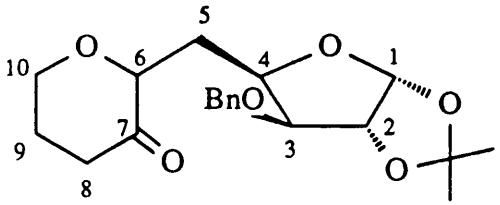

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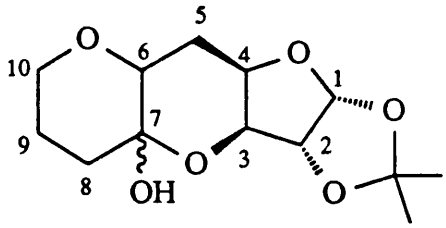
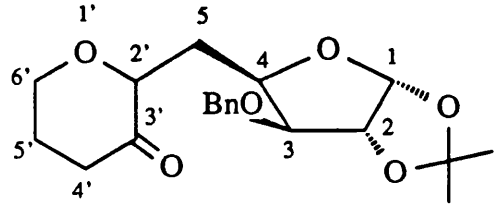


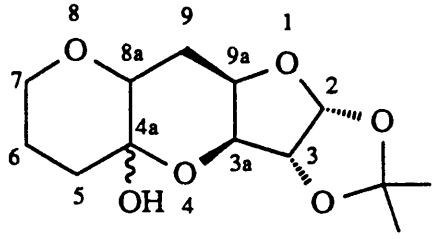
8

It should be noted that the numbering of compounds such as 7 and 8 is based on that used for the herbicidins. This convention has been used throughout the discussion of chapters 1 and 2 and in the experimental section when interpreting n.m.r. data. However, systematic names based on the numbering systems shown in structures 9 and 10 have been provided.



5-(3-oxotetrahydropyran-2-yl)-α-D-xylose

9



furo-pyrano-pyran-4a-ol

10

When referring to a given structure the following abbreviations have been used;-

C(1) - carbon at position 1

C(1)H - proton at carbon 1

C(1)Hax - proton at carbon 1 with axial (Heq-equatorial) configuration

C(1)Hs - This abbreviation has been used when there is more than one proton at a given carbon centre.

These abbreviations have been used extensively in the experimental section when interpreting n.m.r. spectra.

CONTENTS

1. INTRODUCTION

INTRODUCTION

1.1 THE HERBICIDINS (GENERAL CONSIDERATIONS)

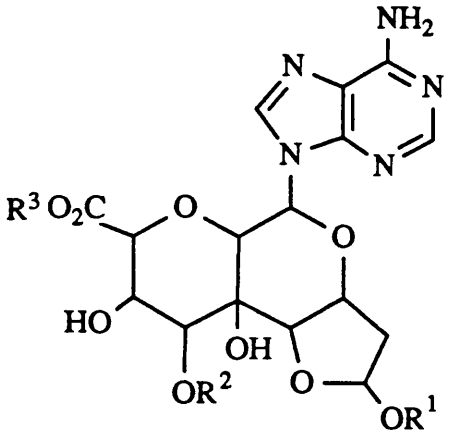
Tetrahydropyrans bearing a C(2)-substituent bonded through carbon may be formally classified as *C*-pyranosides.

Such polyoxygenated *C*-pyranosides have been identified as characteristic components of a plethora of structurally diverse natural products, often occurring multiply within a given compound, either as single units or within fused polycyclic systems. Of the most striking recent examples are palytoxin[1] with eight *C*-pyranoside fragments and brevetoxin[2] with eleven fused rings, eight of which are pyranosides.

The structural complexity and biological properties of these compounds has initiated considerable effort directed towards their synthesis. Relevant aspects of this synthetic chemistry will be discussed below.

One small but structurally unique group of *C*-pyranosides (of the fused type) are the herbicidins. They were isolated[3] following fermentation of a culture identified as *Streptomyces saganonensis*[4]. Structure 1 was originally proposed for the group based on spectroscopic evidence and chemical degradation studies[5]. Subsequent X-ray crystallographic analysis prompted revision of the structure to 2, with the unprecedented furo-pyrano-pyran ring system unequivocally assigned[6].

The herbicidins exhibit herbicidal activity, but have shown little significant antimicrobial activity[4]. Although standing in marked contrast to those nucleoside antibiotics associated with potent antiviral, antifungal, antibacterial and antiparasitic activities e.g. sinefungin[7], the compounds are still of much interest. They are markedly less toxic than most nucleoside antibiotics and presumably exert their herbicidal activity via a novel, though yet unknown, mechanism.



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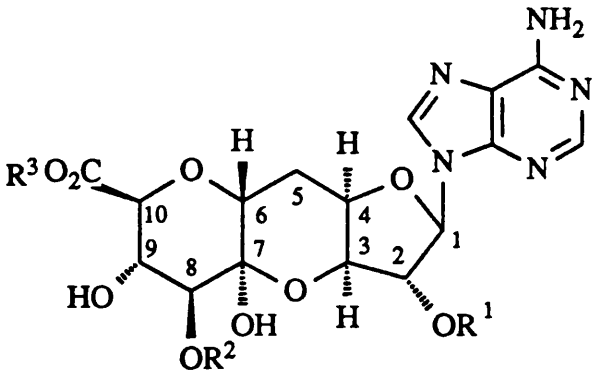


2

	R^1	R^2	R^3
Herbicidin A	CH_3	$CO(CH_2OH)C{=}CHCH_3$	CH_3
Herbicidin B	CH_3	H	CH_3
Herbicidin E	CH_3	$COCH(CH_3)_2$	CH_3
Herbicidin F	CH_3	$CO(CH_3)C{=}CHCH_3$	CH_3
Herbicidin G	H	$CO(CH_3)C{=}CHCH_3$	H

(Note alkenes have (*E*)-geometry)

The aim of this project was to develop not only an expedient synthesis of herbicidins in quantities sufficient for further biochemical investigation, but also to develop methods that would facilitate structural modifications to provide analogues for screening as potential antimicrobial agents. Ideally, these analogues would retain the low toxicity exhibited by the herbicidins.

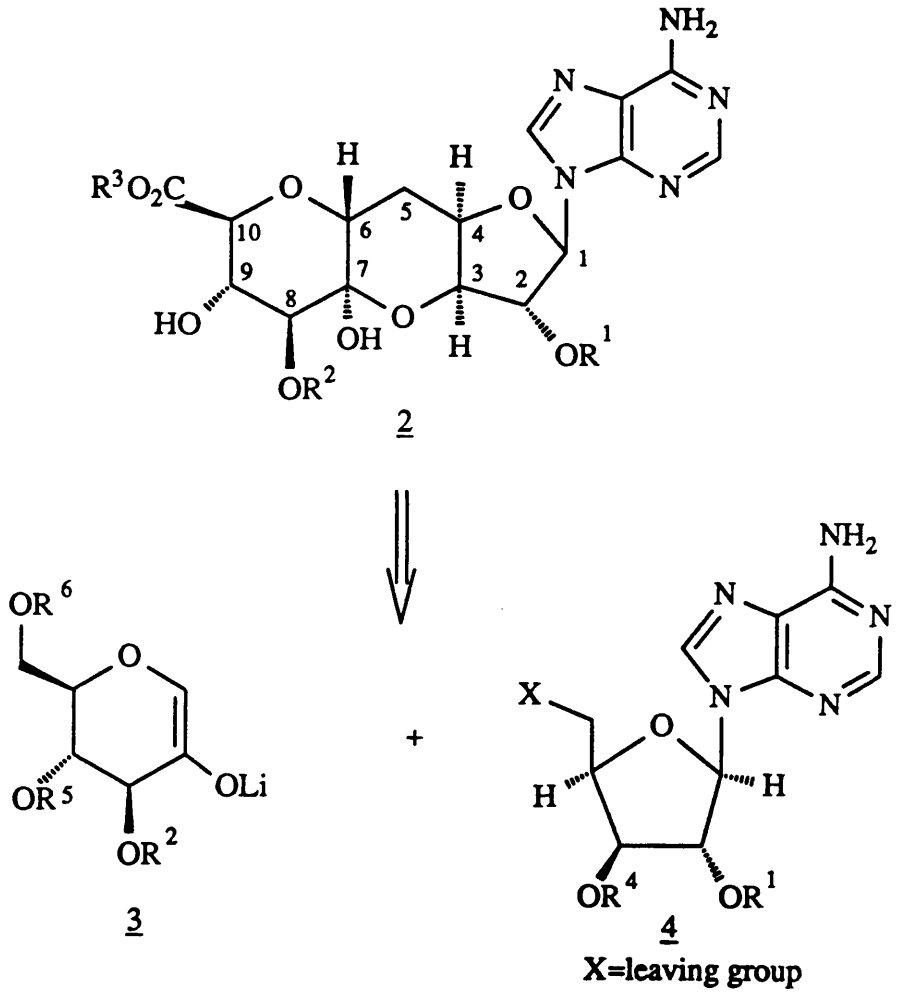
1.2 RETROSYNTHETIC ANALYSIS

Scrutiny of the herbicidin structure **2** reveals a *C*-pyranoside linkage C(6)-C(5)[8]

adjacent to a hemiketal function C(7). Utilising the carbonyl equivalence of the latter function, the carbohydrate-derived enolate 3 and the furanoid electrophile 4 emerge as logical precursors of 2 (Scheme 1).

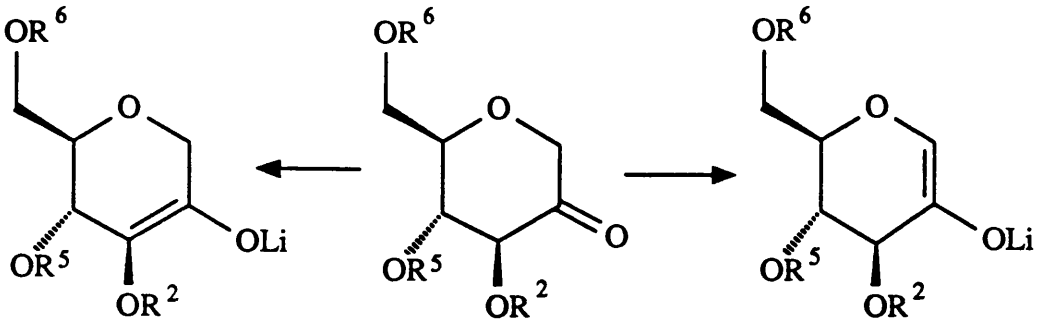
For herbicidin synthesis, the purine moiety, here adenine, could feasibly be incorporated either before (as Scheme 1) or after coupling of the pyranoid and furanoid synthons. Methodology for nucleoside preparation via introduction of protected heterocycles into the anomeric centre of ribose derivatives is both long-established and well documented[9].

Scheme 1



Enolate 3 might be derived from ketone 5 (Scheme 2) which in turn should be available from glucose[10]. In addition, 4 may be conveniently prepared from either glucose or xylose[11]. The fact that starting materials are both readily and cheaply available adds to the general attraction of this convergent approach. Ketone 5,

Scheme 2



6 5 3

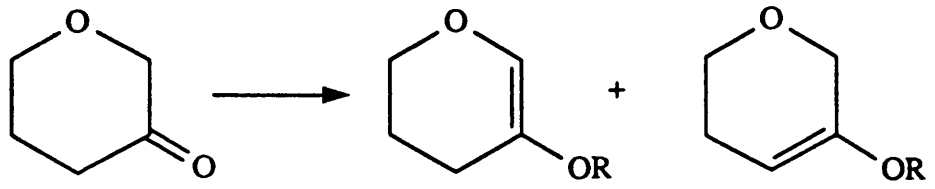
however, is unsymmetrical and is thus also capable of enolisation away from the ring-constrained heteroatom. This would lead to **6**. To date, the mode of enolisation of systems such as **5** has not been studied in detail. However, precedent exists for related 3-keto-pyranosides, in which deprotonation occurs almost exclusively at the position remote from the pyran oxygen to give the "undesired" enolate[12], e.g. **6**. Since all these examples differ from **5** in both stereochemistry of, and level of substitution around the carbonyl group, confident predictions concerning deprotonation of **5** are precluded.

Considering inductive effects alone, an oxygen substituent might be expected to stabilise an adjacent carbanion. Calculations performed by Lehn[13] predict 10-15 kcal/mole stabilisation relative to a methylene group. These results are in accord with the experimental observations of McGarvey[14].

Molecular mechanics calculations have shown that enol acetate **8** (Scheme 3) is conformationally more stable than **9**[15].

Based on these conformational and inductive effects, **8** might be expected as the major product of enolisation of **7**, especially under conditions favouring thermodynamic control. Experimentally, however, **9** was found to be the major product under both kinetic and thermodynamic control[15,16]. The variance between calculated and experimental results has been attributed to unfavourable stereoelectronic repulsions between unshared electron pairs of the carbanionic centre

Scheme 3



7 8 9

R=Ac	Kinetic	24%	76%
	Thermodynamic	-	100%
$R=SiMe_3$	Kinetic	25-12%	75-88%
	Thermodynamic	11%	89%

and those of the conformationally constrained ring oxygen being greater than the favourable inductive and steric effects.

Hine has shown that this destabilising effect can be minimised through rotation about the carbon-oxygen bond[17]; a process available to the acyclic oxygen substituent but not to the ring heteroatom.

In total, this evidence would seem to suggest that deprotonation of ketone **5** would result in enolisation away from the pyranoid oxygen to give **6**; i.e. an enolate unsuitable for the proposed synthesis. Therefore, either a synthon for the desired enolate **3** or an alternative method for the regiospecific introduction of a carbon-carbon single bond at the anomeric centre of a pyranose ring is required.

Before discussing our approaches to this problem, it would be prudent to review methods currently available for the preparation of *C*-pyranosides.

1.3 THE SYNTHESIS OF *C*-PYRANOSIDES

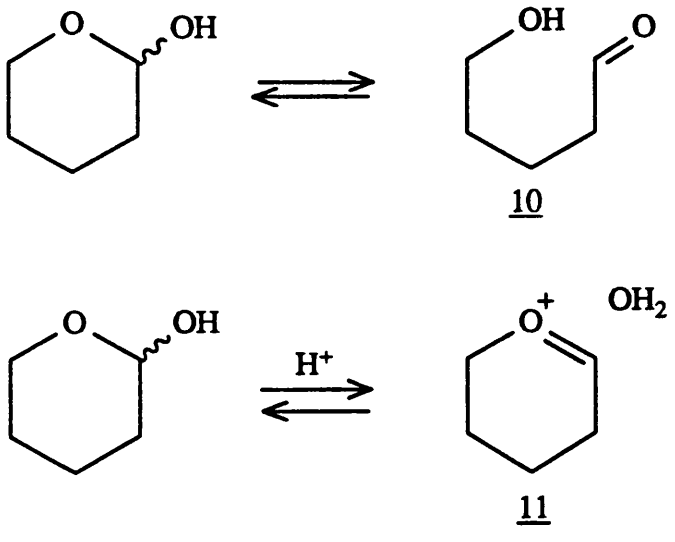
As intimated above, the synthesis of C(2) carbon-substituted pyranoid and furanoid units has gained increasing importance in recent years, not only because of interest in medicinally important *C*-nucleosides but also as a result of the diverse array of biologically interesting natural products which contain these subunits. Furthermore, chain-extended carbohydrates are also useful as chiral templates for other synthetic objectives.

A review of all endeavours in this area is not relevant to this thesis. Fortunately, however, useful reviews have appeared recently which successfully cover the *C*-nucleoside area[18], the synthesis of polyether antibiotics[19] and the preparation and use of chiral templates[20].

This review will concentrate on methods of introducing carbon-carbon bonds to the "anomeric" centre of pyranose rings.

The reactivity of hemiacetals is generally that of an electrophile. This derives not only from the carbonyl equivalence of the "anomeric" centre (**10**, Scheme 4) but also from the ease with which the oxonium ion **11** can be generated (Scheme 4). As

Scheme 4



a consequence many methods are available for the introduction of nucleophiles to pyranose rings. This mode of reactivity does, however, have its limitations and recently interest has centred on inverting the polarity of the "anomeric" centre via the generation of either radicals or anions at this centre.

This review is, therefore, divided into three sections;

a) The introduction of nucleophiles to the anomeric centre.

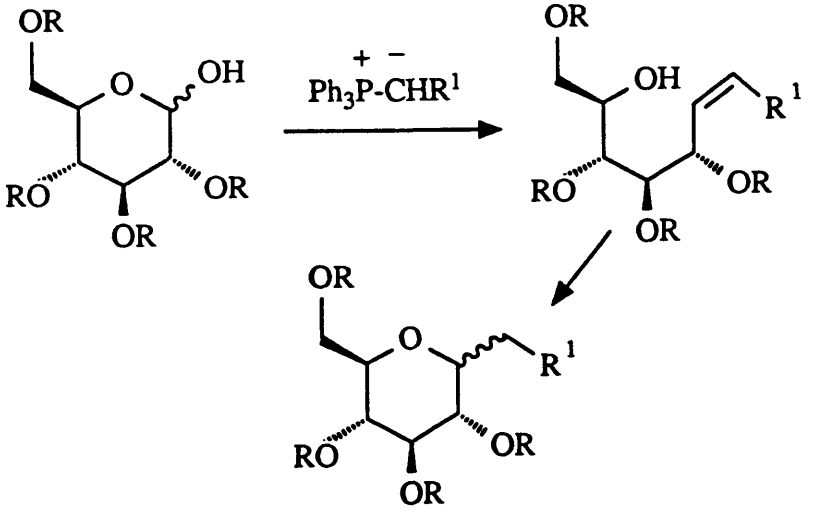
b) The generation and reactivity of anomeric radicals.

c) The generation and reactivity of anomeric anions.

1.3a The introduction of nucleophiles to the anomeric centre

As described above, pyranose rings have aldehyde reactivity. Hence their reactions with Wittig reagents is well established[21] (Scheme 5).

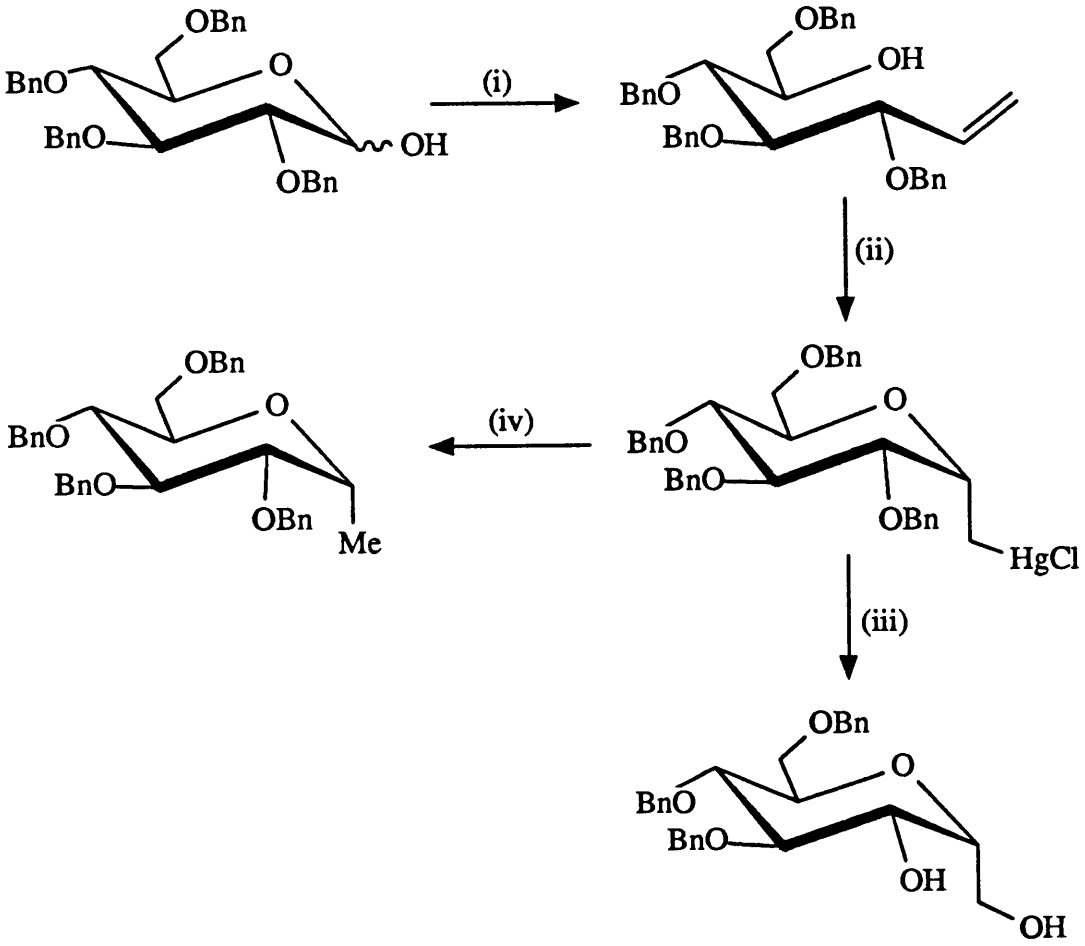
Scheme 5



It will become apparent throughout this discussion that emphasis is now placed on stereocontrolled routes to α- and *β-C*-pyranosides. This trend is reflected in two recent applications of the Wittig methodology.

Sinaÿ[22] has developed a stereoselective route to α-D-*C*-glucopyranosyl derivatives using a Wittig reaction followed by a mercuricyclisation (Scheme 6).

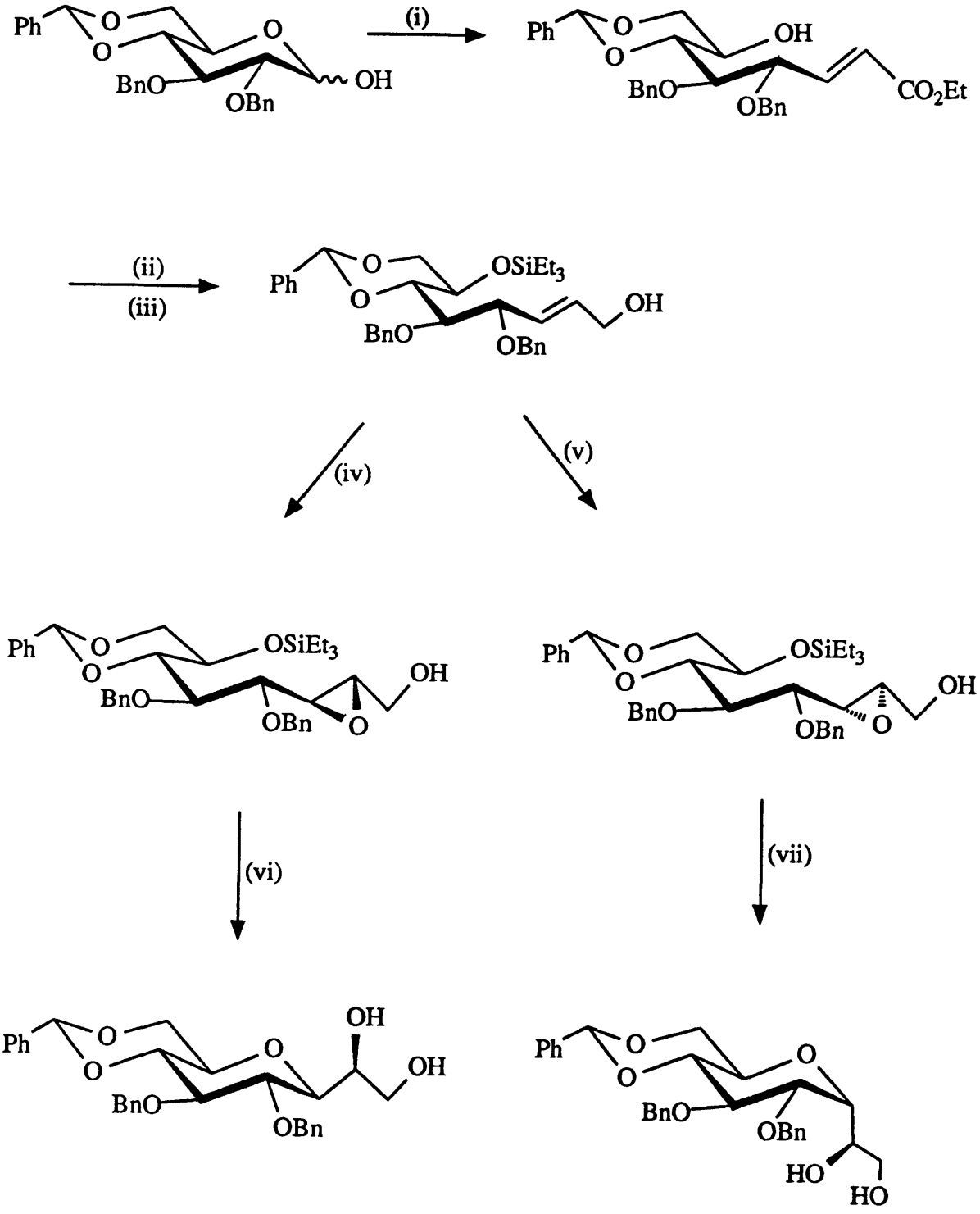
Scheme 6



Reagents (i) $Ph_3P^+Me\ Br^-$,*n*-BuLi, (80%); (ii) $Hg(OAc)_2$, (98%); (iii) O_2, $NaBH_4$; (iv) $NaBH_4$.

A more versatile methodology has been developed by Sharpless and Masamune[23], which provides access to both α and β-anomers stereoselectively. Following a Wittig reaction, the method uses titanium-catalysed asymmetric epoxidation with diethyl (+)- or (-)- tartrate (DET) to create the crucial C(2) centre of the tetrahydropyran system (Scheme 7).

Scheme 7

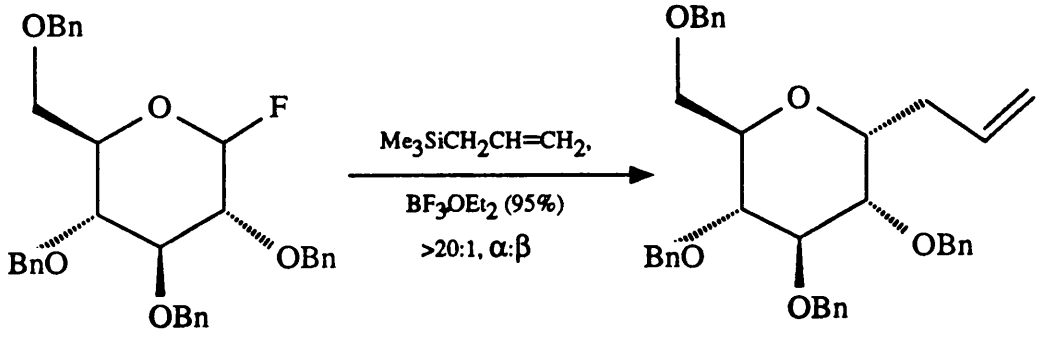


Reagents (i) $Ph_3P{=}CHCO_2Et$,(84%); (ii) Et_3SiOTf; (iii) DIBAL, (96%,two steps); (iv) (+)-DET, (88%); (v) (-)-DET(96%); (vi) a) TBAF, b) NaH,DMF(80%); (vii) a) TBAF, b) NaH,DMF(85%).

Treatment of a glycoside with either hydrochloric or hydrobromic acid results in smooth formation of the corresponding glycosyl halide. Displacement of bromide and chloride from the anomeric centre with a carbon nucleophile has thus been used extensively in *C*-pyranoside synthesis[18]. Until recent developments made them more accessible, the corresponding glycosyl fluorides[24], however, had received relatively little attention.

Nicolaou has demonstrated that glycosyl fluorides will react with a number of nucleophilic reagents, including allyl silanes, silyl enol ethers and organoaluminium reagents with or without Lewis acid catalysis to give a variety of *C*-glycosides[25]; e.g. Scheme 8.

Scheme 8

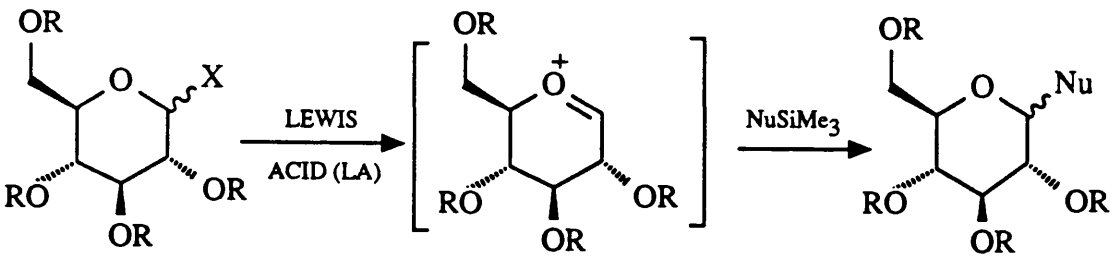


This chemistry is applicable to both mono- and disaccharides and generally gives the α-anomer predominantly.

Also taking advantage of the strong affinity of aluminium for fluoride ions, Posner has synthesized *C*-pyranosides via the action of an organoaluminium reagent on a glycosyl fluoride[26].

As described above, cyclic oxonium ions such as 13 (Scheme 9) can be easily generated via treatment of a suitable glycosyl derivative 12 with a Lewis acid. Various methods have been employed to perform this transformation and trap the intermediate oxonium ion with a silylated nucleophile, as summarised in Table 1.

Scheme 9



12 13 14

Table 1

Leaving group X	Lewis Acid (LA)	Nucleophile Nu	Selectivity $\alpha:\beta$	Ref
OMe	TMSOTf	Allyl	1:0	35,27
Cl	TMSI	Allyl	10:1	27
	AgOTf	Enol Ether	1:0	28
OPNB	$BF_3.OEt_2$	Allyl	1:0	29,30
	$ZnBr_2$	Allyl	5:1	30
OBn	$BF_3.OEt_2$	Allyl	10:1	29
OAc	$ZnBr_2$	Allyl	4:1	31
	$BF_3.OEt_2$	Allyl	95:5(best)	30,32,33
	$ZnCl_2$	Allyl	4:1(best)	30
		Enol Ether	1:0	34
	TMSOTf	Allyl	1:0	30
OTCAI	$ZnCl_2$	Allyl	1:0	36
	$ZnCl_2$	Enol Ether	1:0	36
	TMSOTf	CN	1:0	37
SPy	AgOTf	Enol Ether	1:0	38
$OCOCF_3$	$BF_3.OEt_2$	Various	1:0	39

Note: Table 1 refers to carbohydrate precursors other than glucosyl derivatives 12 (Scheme 9).

OPNB = *O-para*-nitrobenzyl

OTCAI = *O*-trichloroacetimidate

SPy = thiopyridyl

In the vast majority of cases there is a predominance of the α-anomer in product mixtures and in some cases its formation is exclusive.

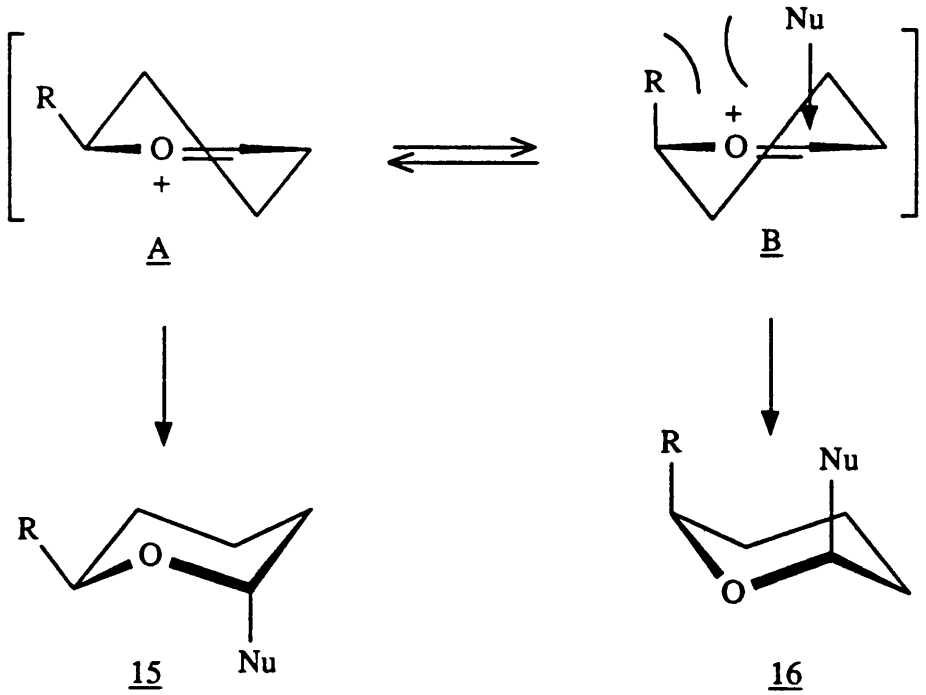
Kishi has explained this stereoselectivity as arising from two factors[29,34] (Scheme 10):

1) A stereoelectronic effect; i.e. the nucleophile is introduced antiperiplanar to one of the ring oxygen lone pairs.

2) Steric hinderance, arising from the R group in conformer B (Scheme 10), thus providing the product **15** having the experimentally observed stereochemistry.

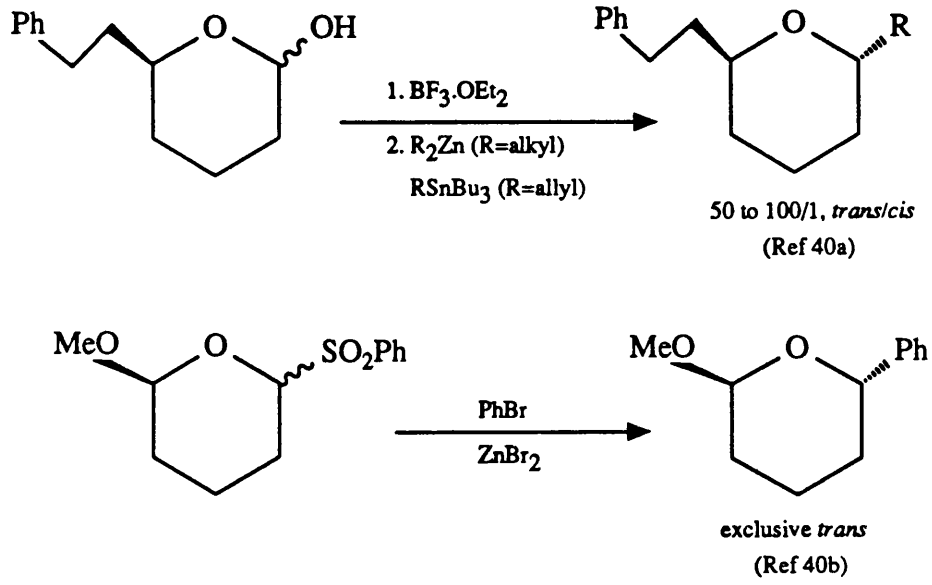
Variation in stereoselectivity is presumably dependent on additional ring substituents and the extent to which the reaction follows an S_N1 mechanism.

Scheme 10



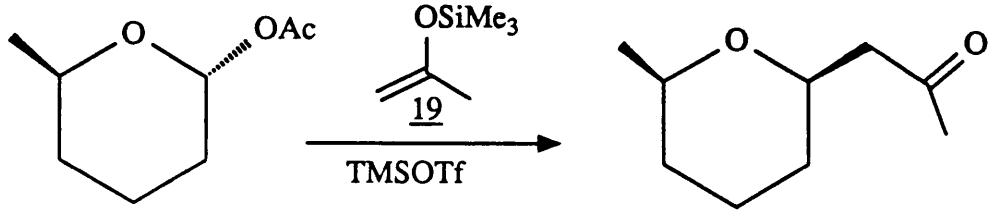
Similar stereoselectivity has been observed in the reactivity of mono-substituted tetrahydropyrans[40], e.g. Scheme 11.

Scheme 11



In contrast to these results, Noyori[41] has prepared the *cis*-2-6-disubstituted tetrahydropyran **18** (Scheme 12) via condensation of the 2-acetoxytetrahydropyran **17** with silyl enol ether **19** in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf). This selectivity has been rationalised in terms

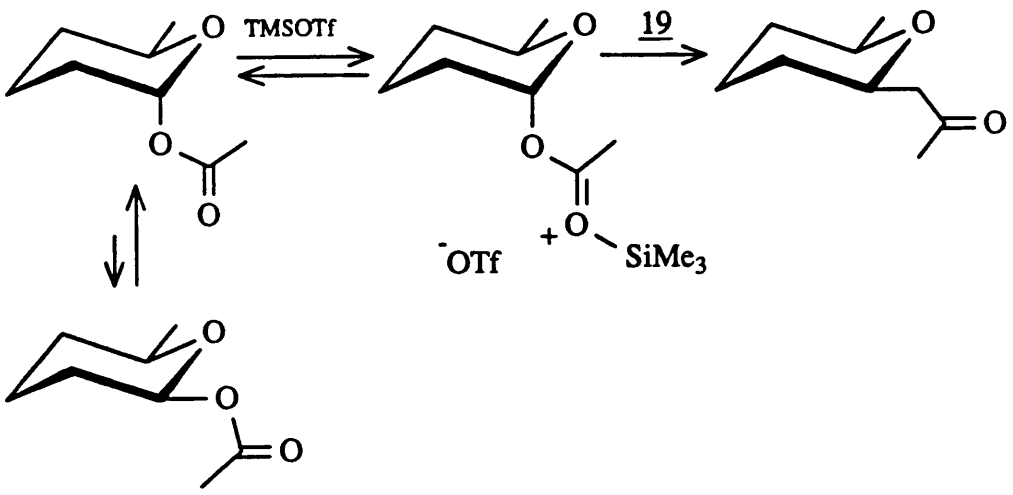
Scheme 12



17 18

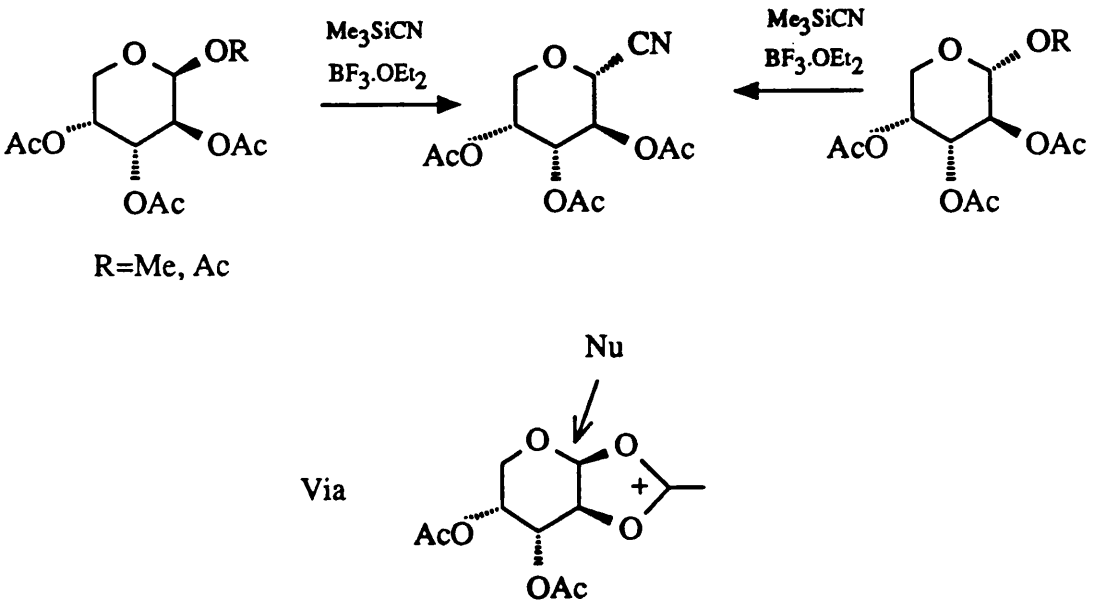
of an S_N2 displacement of the kinetically labile axial acetate by the silyl enol ether, aided by the TMSOTf (Scheme 13).

Scheme 13



The neighbouring group effect of the acetate unit is well established in the stereoselective synthesis of *C*-nucleosides and *C*-glycosides (for example see ref 18). This effect has recently been used to control the introduction of a cyanide group to the anomeric centre of a methyl or acyl-glycoside using trimethylsilylcyanide (TMSCN) and a Lewis acid catalyst[42], e.g. boron trifluoride etherate ($BF_3.OEt_2$), as shown in Scheme 14.

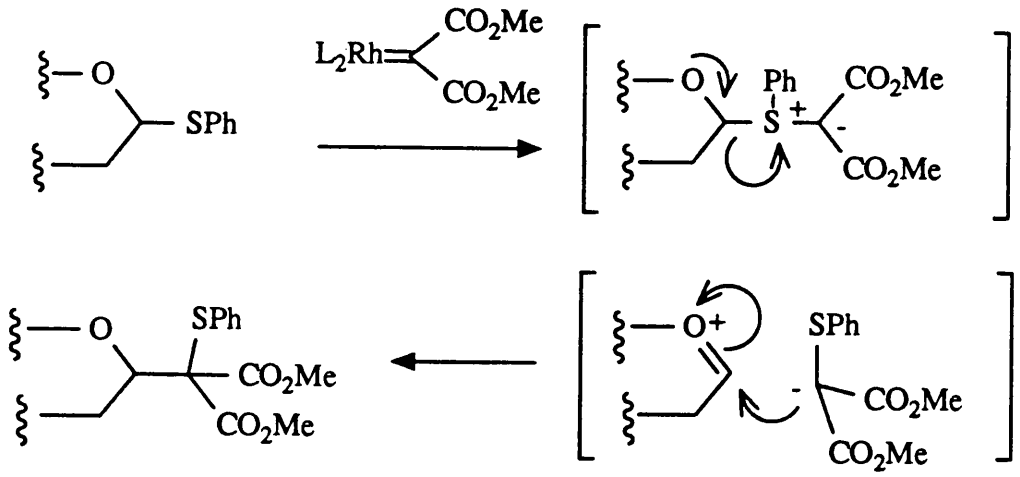
Scheme 14



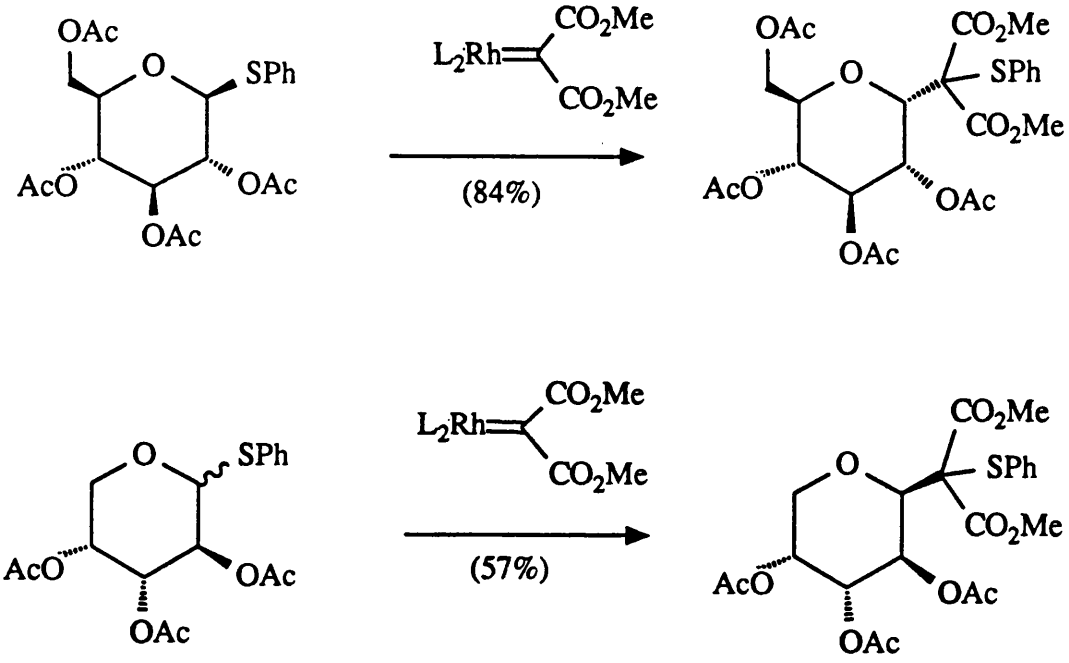
During a recent study, Kametani found that a neighbouring acetate group can also participate in the introduction of a carbon-carbon bond *syn* to itself[43]; i.e. complementing the stereochemistry shown in Scheme 14. The study was aimed at the stereoselective formation of *C*-pyranoside bonds by means of a carbenoid displacement reaction on a phenylthioglycoside as outlined in Scheme 15.

Although successful, the procedure was found to be most efficient and stereoselective when the carbohydrate substrate contained acyl protection as demonstrated by the two examples of Scheme 16.

Scheme 15

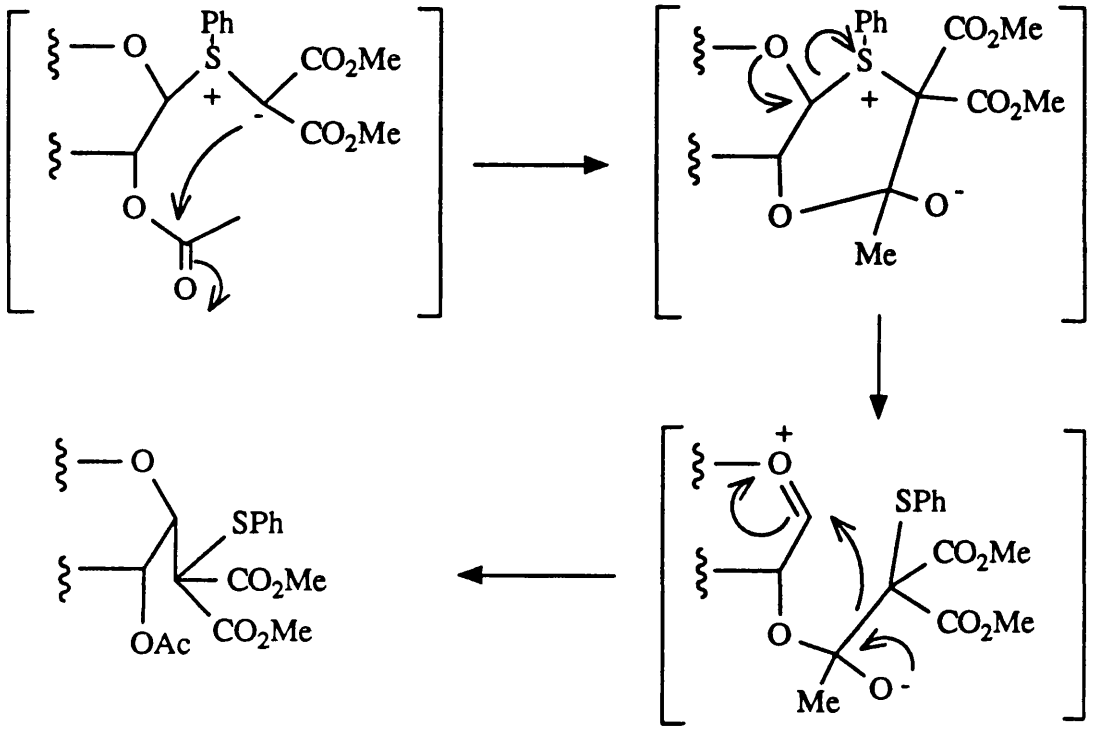


Scheme 16



The mechanism shown in Scheme 17 has been proposed to explain these experimental findings.

Scheme 17

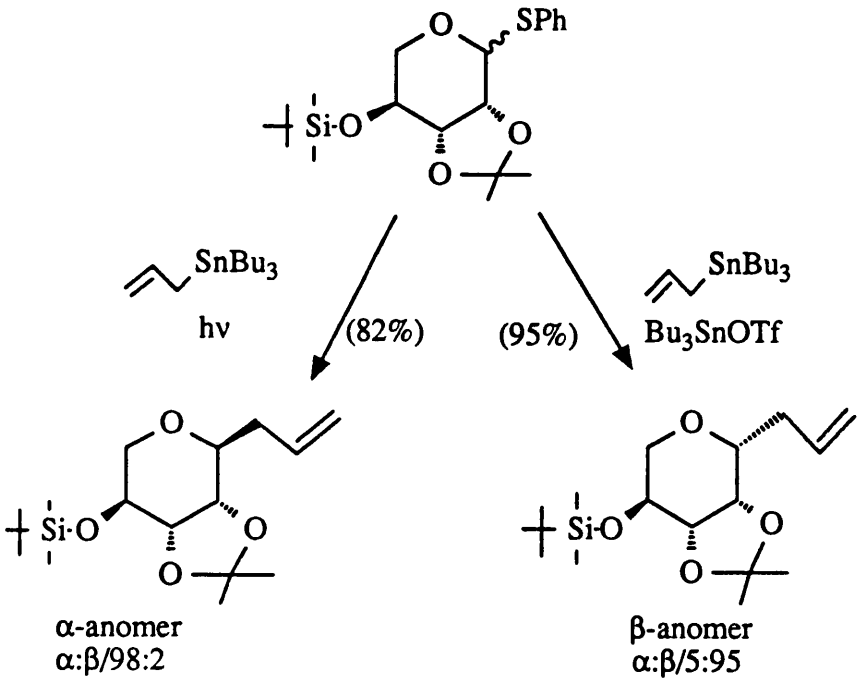


Phenylthioglycosides have also been used by Keck[44] for the regiospecific preparation of *C*-pyranosides using either tributylstannyltriflate and allyl stannane or photolysis in the presence of allyl stannane. Both methods are high yielding and show significant levels of stereoselectivity in certain cases (Scheme 18). Unfortunately, this selectivity does not translate to all thioglycosides.

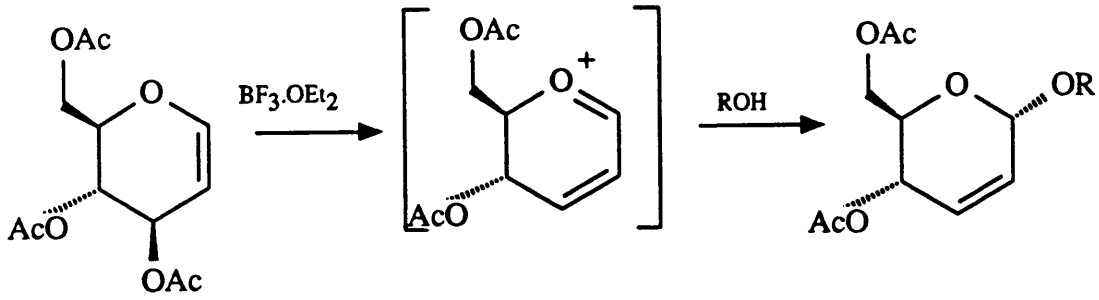
Many of the methodologies discussed thus far are also applicable to the synthesis of *O*-glycosides. One method which almost certainly draws its inspiration from *O*-glycoside synthesis is the carbon-Ferrier reaction. Ferrier discovered that treatment of glycals such as 19 with Lewis acids followed by addition of an alcohol led to 3,4-unsaturated glycosides 21[45], presumably via the allyl-oxonium ion 20

(Scheme 19).

Scheme 18



Scheme 19

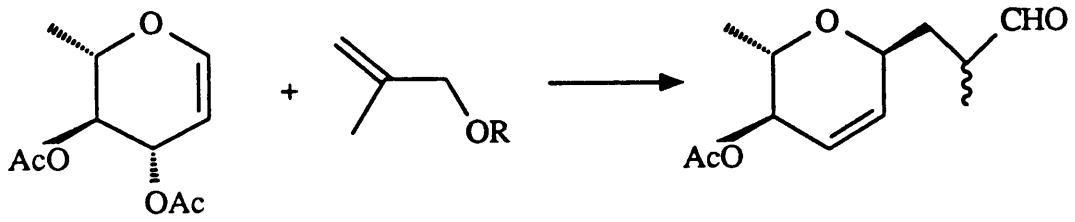


19 20 21

In recent years, efforts have been directed towards the regiospecific trapping of the cation 20 with carbon nucleophiles.

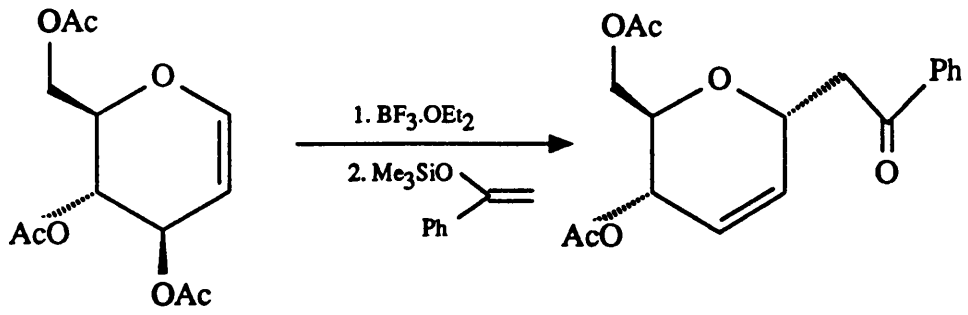
Amongst the species investigated as nucleophiles have been β-diketones[46] and alkenes[47]. Herscovici showed that protected allylic alcohols can be used as homoenolate equivalents[48] as shown in Scheme 20.

Scheme 20



Silylated nucleophiles have also been used including silyl enol ethers[49] and allyl silanes[50,51]. The best Lewis acid for use with these nucleophiles was found to be $BF_3.OEt_2$ and, as with most of the examples given above, reactions were stereoselective with the new group emerging at C(2) in a *trans*-relationship to C(6) as in Scheme 21.

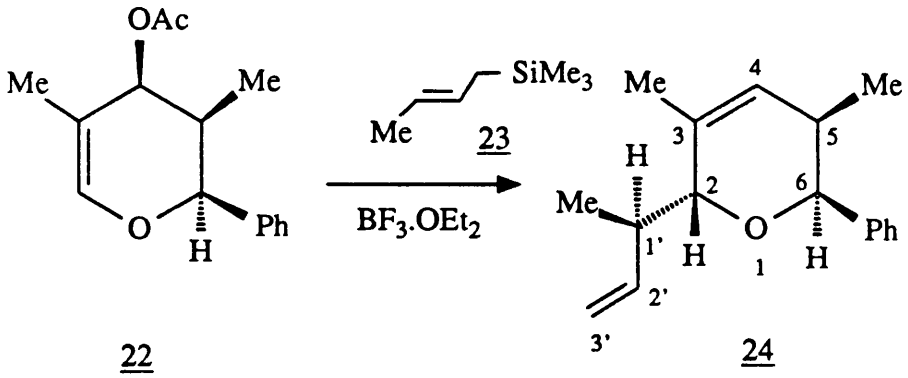
Scheme 21



In what amounts to the most extensive study of the carbon-Ferrier reaction[51], Danishefsky has demonstrated that in the addition of allyl silanes to allyl-oxonium

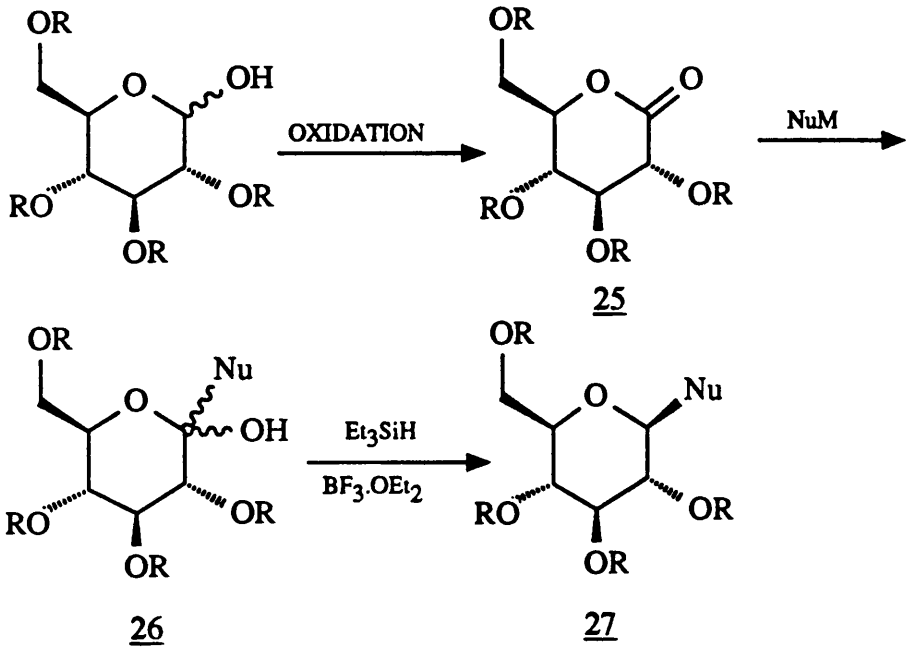
ions the stereochemistry at C(1') can be controlled along with that at C(2). The stereocontrol at C(1') is dependent on the C(3) substituent and the geometry of the allyl silane, whilst entry to the C(2), C(6)-*trans* product is stereospecific under the reaction conditions. Thus reaction of (*E*)-crotyl silane **23** with the C(3) methylated glycal **22**, in the presence of $BF_3.OEt_2$, gives a 30:1 mixture of products in 67% yield, where **24** is the major product and the minor product is the epimer at C(1').

Scheme 22



Oxidation of an hemiacetal provides the corresponding lactone, a species which can also be used as an electrophilic precursor to *C*-pyranosides, e.g. Scheme 23.

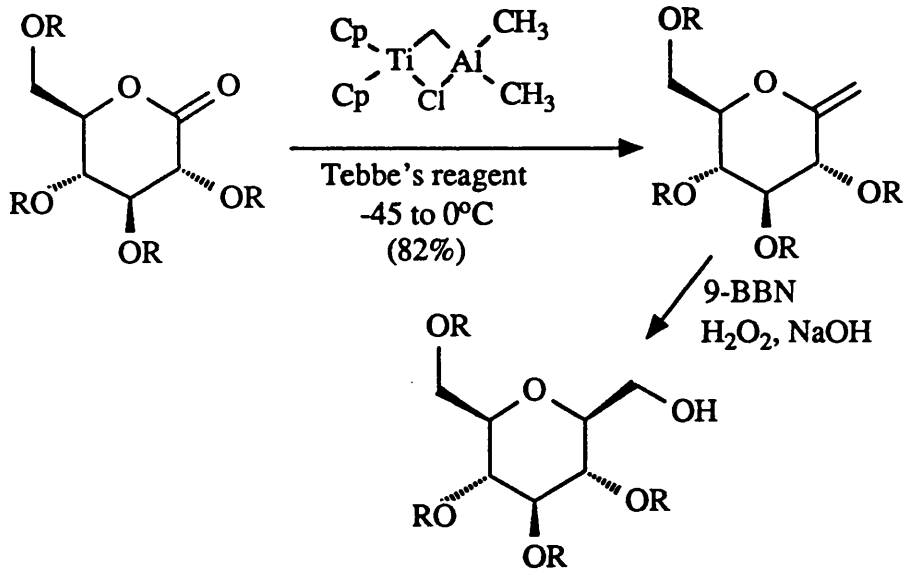
Scheme 23



Treating a glycosyl lactone (25) with an alkynyl[52]/aryl lithium[53] or Grignard[29,53] reagent (NuM) provides an anomeric mixture of hemiketals 26. These compounds can then be reduced stereospecifically, using conditions first established by Kishi[29] (Et_3SiH, $BF_3.OEt_2$,MeCN), to give the β-D-*C*-glycoside 27. This technology has subsequently been used by Kraus[53] (vinyl and aryl glycosides), Sinaÿ (ambruticin[52] and *C*-disaccharide synthesis[54]) and in further studies by Kishi[55] (*C*-disaccharides) in stereospecific β-*C*-pyranoside synthesis.

Glycosyl lactones can also be methylenated[56] using a metal carbene complex (Tebbe's reagent). Hydroboration of the resulting enol ether with the sterically demanding 9-borabicyclo[3.3.1]nonane (9-BBN) then provides β-*C*-pyranosides stereospecifically[56b] (Scheme 24).

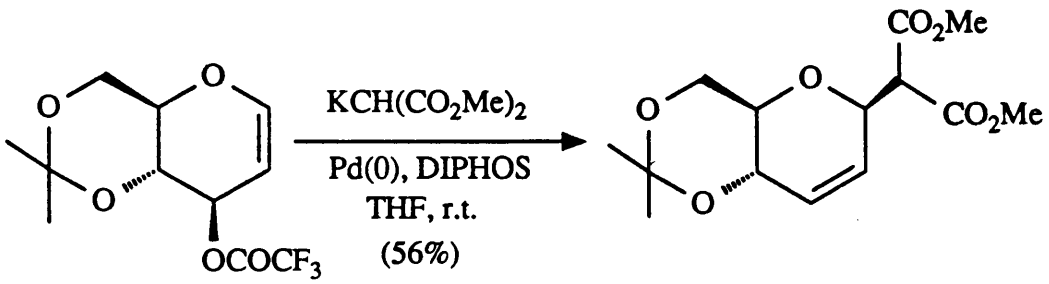
Scheme 24



Organotransition metals have also been used extensively in *C*-pyranoside synthesis. Organopalladium addition reactions to glycals have been studied in depth by Daves[57]. Also studied has been the palladium (0) catalysed addition of nucleophiles to pyranoses containing allylic-*O*-acetate groups[58]. This transformation

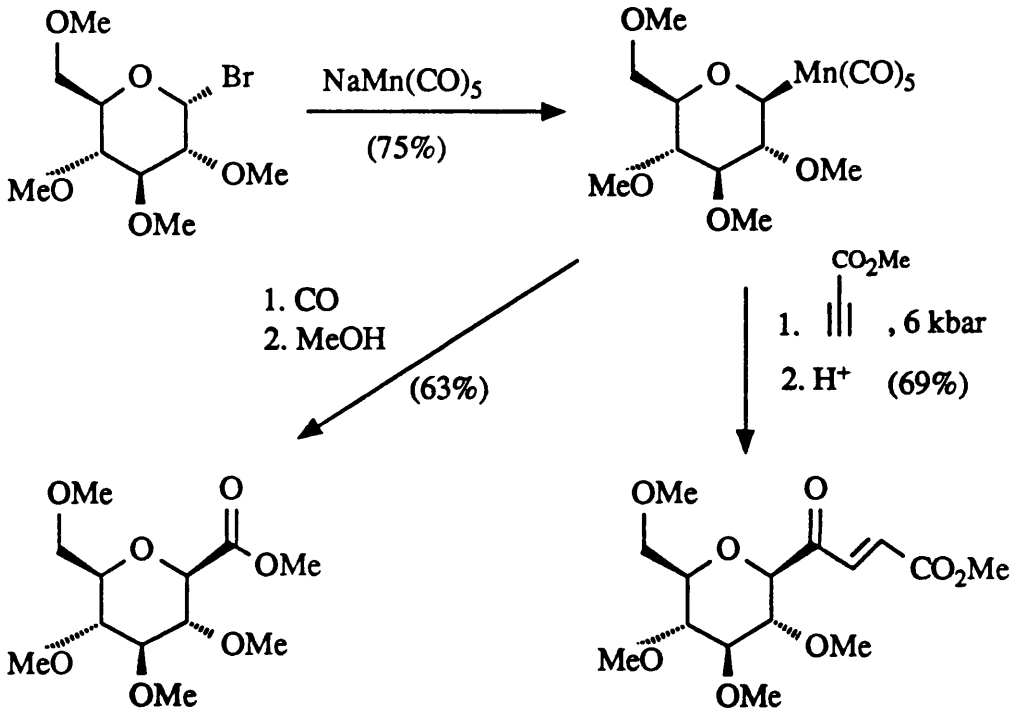
amounts to a carbon-Ferrier reaction with opposite stereoselectivity as can be seen in Scheme 25.

Scheme 25



An alternative use of transition metals involves the preparation of either glycosylcobalt tetracarbonyl[59] or glycosylmanganese pentacarbonyl[60] complexes. Carbonylation of these complexes, with retention of configuration, followed by either reduction or ligand incorporation results in the stereoselective formation of *C*-pyranosides, e.g. Scheme 26.

Scheme 26



1.3b The generation and reactivity of anomeric radicals

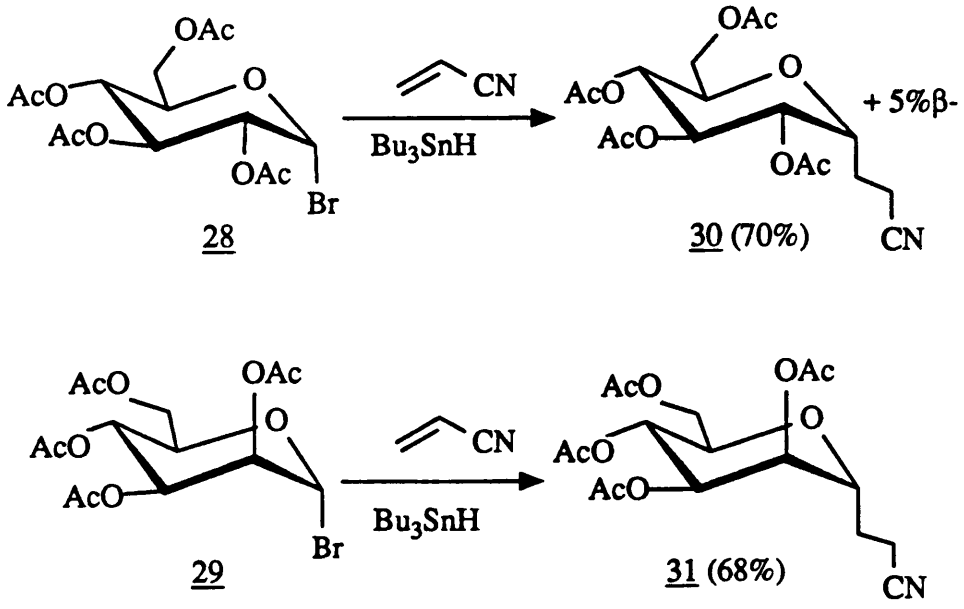
The use of radicals in the formation of carbon-carbon bonds offers a useful alternative to ionic reactions[61]. For example, radicals often provide different chemoselectivity and regioselectivity as well as an "umpolung" of the reactivity at a certain centre. It is not surprising then, that the formation and reactivity of radicals at the anomeric centre of pyranose rings has been studied in some detail.

Anomeric radicals are most often generated from the glycosyl bromide or chloride via photolysis or thermolysis in the presence of tributyltin hydride[62]. Vitamin B_{12} in the presence of zinc has also been used to homolyse a glycosyl halide bond[63].

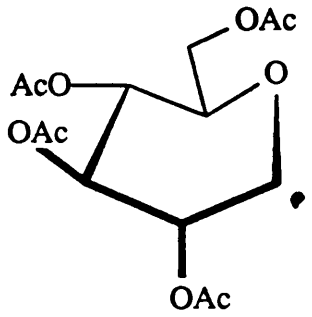
Alternative methods have used glycosyl fluorides ($MgBr_2$,Bu_3SnH,$h\nu$)[25], glycosyl selenides (Ph_3SnH,Δ)[62b], glycosyl sulphides (Bu_3SnH,$h\nu$)[44] and glycosyl nitro derivatives (Bu_3SnH,Δ)[64].

Common electrophiles have been acrylonitrile, enones, H$^{\bullet}$(Bu_3SnH) and D$^{\bullet}$(Bu_3SnD). In all cases, α-addition of electrophile predominates, often exclusively. Two examples involving glucosyl (**28**) and mannosyl (**29**) radical precursors are shown in Scheme 27.

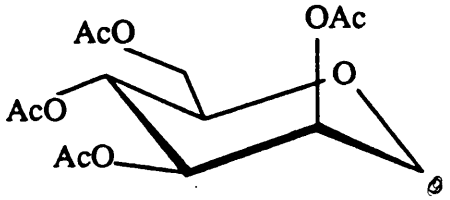
Scheme 27



The predominant formation of α-*C*-glycosides 30 and 31 results from equatorial attack at the boat conformation of the glucosyl radical 32 and from the shielding effect of the axial substituent in the chair conformation of the mannosyl radical 33 respectively[65].



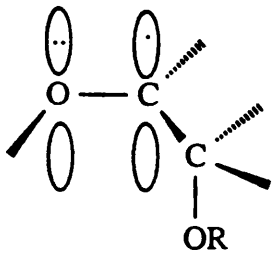
32

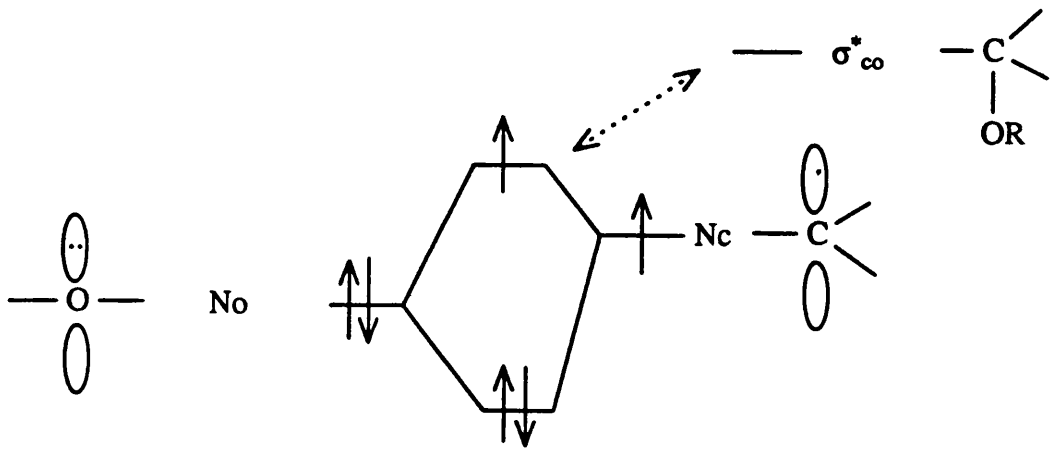


33

The glucosyl radical exists in the boat conformation as this allows an interaction between the high energy SOMO of the alkoxyalkyl radical and the low energy LUMO of the adjacent carbon-oxygen bond (Scheme 28).

Scheme 28

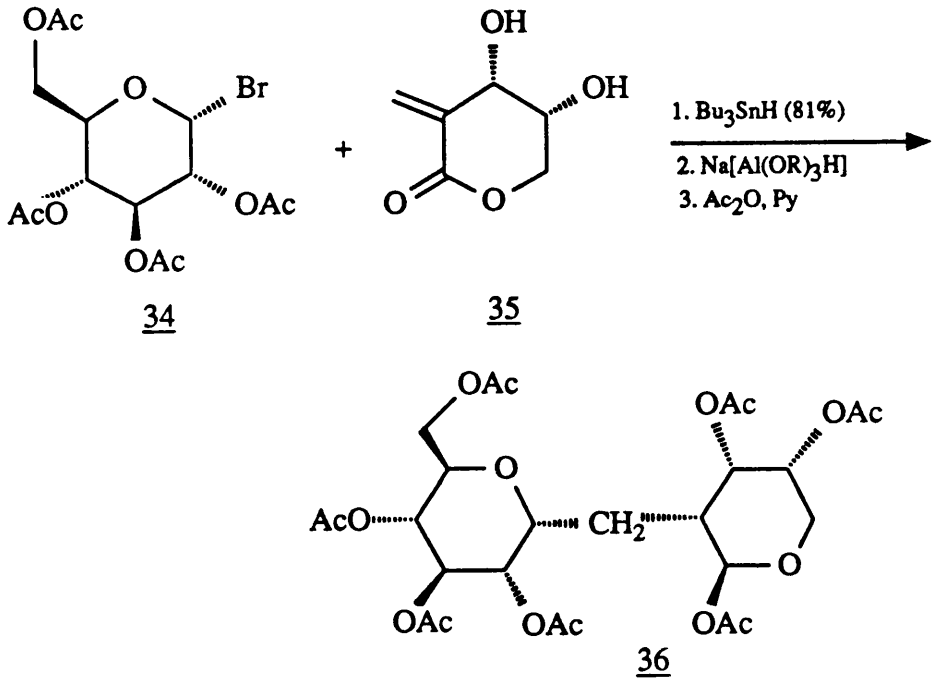




This interaction is possible in the mannosyl radical without major changes in conformation.

Using this methodology *C*-disaccharide **36** (Scheme 29), in which the oxygen atom between the pyranosyl rings of the disaccharide is substituted by a methylene group, is readily available[66] from bromide **34** and alkene **35**.

Scheme 29



34 35 36

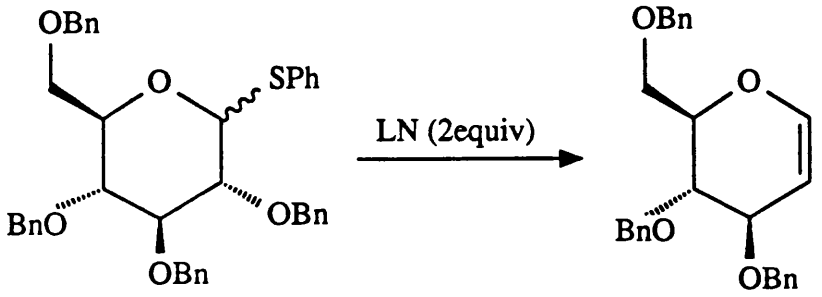
1.3c The generation and reactivity of anomeric anions

Of particular relevance to our synthetic programme is the generation of anions at the anomeric centre of tetrahydropyrans.

The high temperatures required to bring about deprotonation of saturated cyclic ethers generally leads to decomposition of the resulting anion[67]. Methods which employ milder conditions are, therefore, required.

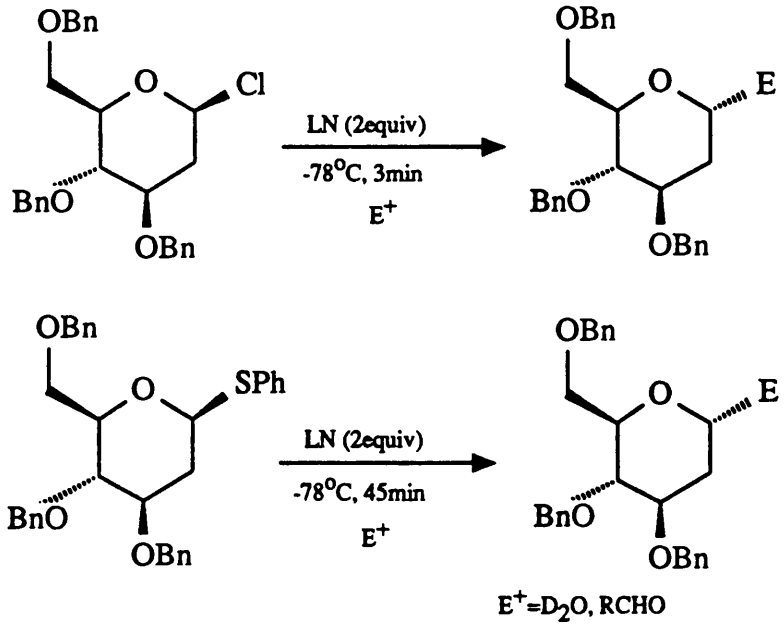
One such mild procedure involves the reductive lithiation of a glycosyl sulphide or chloride with two-equivalents of a one-electron transfer reagent, e.g. lithium naphthalenide (LN). Preliminary studies[68] indicated that the generation of a glycosyl lithium species was prohibited when the pyran contained C(3) oxygen substitution, since β-elimination resulted as illustrated in Scheme 30.

Scheme 30



However, no problems were encountered with C(3)-deoxy-pyranose derivatives as indicated in Scheme 31.

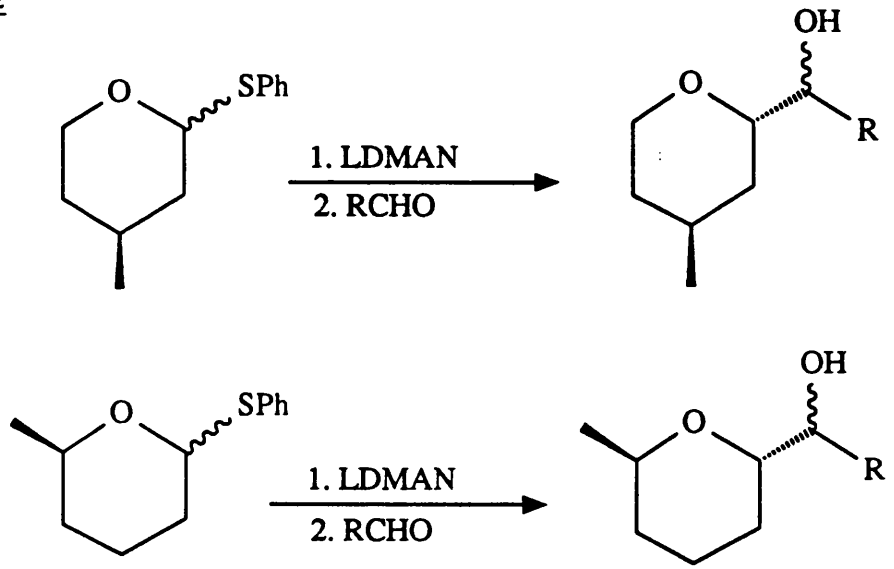
Scheme 31



Electrophiles are introduced exclusively in the axial orientation at -78°C, providing α-*C*-pyranosides stereoselectively from either α- or β- precursors.

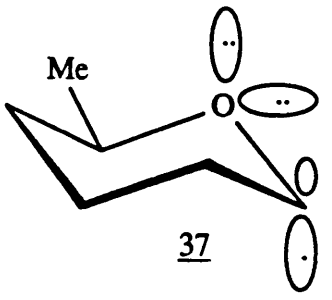
Cohen observed similar stereoselectivity when this reductive lithiation procedure was applied to simple mono-substituted tetrahydropyrans[69], e.g. Scheme 32.

Scheme 32

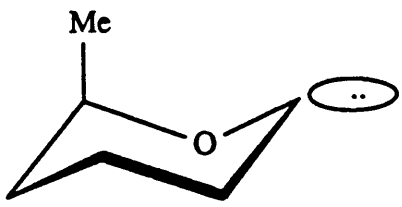


LDMAN=lithium 1-(dimethylamino)naphthalenide

Cohen explained the observed stereoselectivity as arising from the intermediacy of the axial radical 37. This conformation is preferred because of the favourable overlap of the axial oxygen lone pair with the back lobe of the radical orbital. Addition of an electron to this intermediate then provides the axial organolithium. The carbohydrate based organolithiums are conformationally stable at -78°C and



37

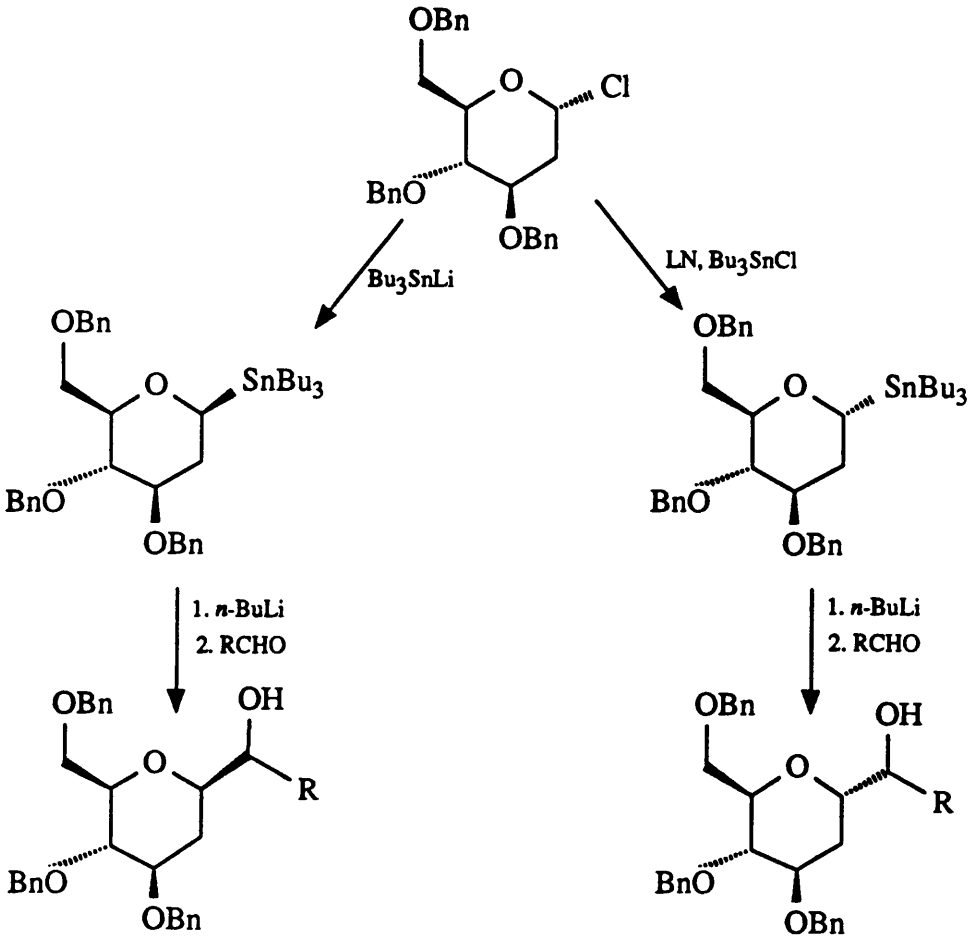


38

provide the α-*C*-pyranosides. The less substituted tetrahydropyran **37** probably undergoes chair-chair interconversion to **38**, thereby attaining the stable equatorial arrangement of the carbon-lithium bond. The *trans* arrangement of the ring substituents, however, is maintained.

A second method for the preparation of glycosyl lithium reagents, under mild conditions, is transmetalation[70]. Hence formation of the α- and β-glycosyl stannanes from the corresponding α-glycosyl chloride, followed by treatment with *n*-butyllithium provides stereoselective access to the α- and β- glycosyl reagents, i.e. transmetalation occurs with retention of configuration. Alkylation of these anions also proceeds with retention to provide α- and β-*C*-pyranosides as outlined in Scheme 33.

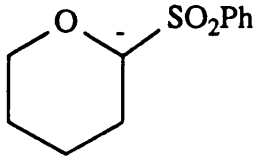
Scheme 33



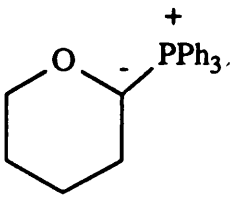
The generation of glycosyl cuprates derived from the transmetalation of glycosyl stannanes and their alkylation with enones also proceeds with retention of configuration[71].

An alternative strategy for the formation of anomeric anions utilises the acidifying effect of an adjacent electron-withdrawing group. Hence species such as **39- 43** (Scheme 34) have been used to introduce *C*-pyranoside bonds[72-76]. Although all but the Horner-Wittig reagent **41** have applications in the carbohydrate area, only the glycosyl nitro derivative **42** has been used successfully with C(3)-oxygen substitution.

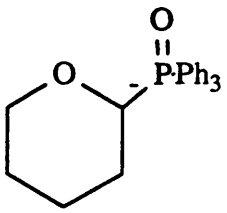
Scheme 34



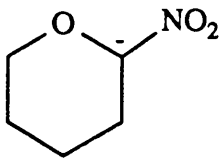
39 (ref 72)



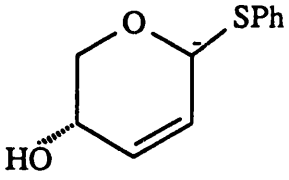
40 (ref 73)



41 (ref 74)



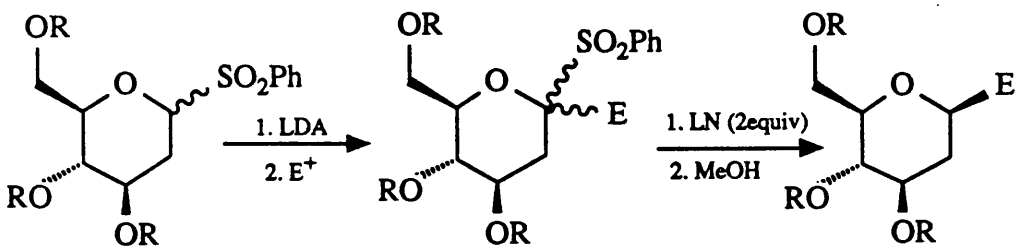
42 (ref 75)



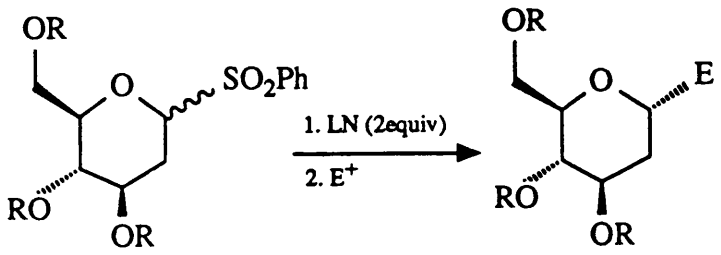
43 (ref 76)

Glycosyl sulphones have established themselves as useful intermediates in *C*-pyranoside synthesis[40b,72] as outlined in Scheme 35. Although introduction of the carbon-carbon bond is not particularly stereoselective (4:1 $\beta:\alpha$), this is of no consequence as reductive removal of the sulphone proceeds stereospecifically[72d] to give the β-*C*-pyranoside **44**. This methodology is complementary to the reductive lithiation of glycosyl sulphides (described above)[68] and glycosyl sulphones (outlined in Scheme 35)[72c] which provides α-*C*-pyranosides (**45**) stereospecifically.

Scheme 35



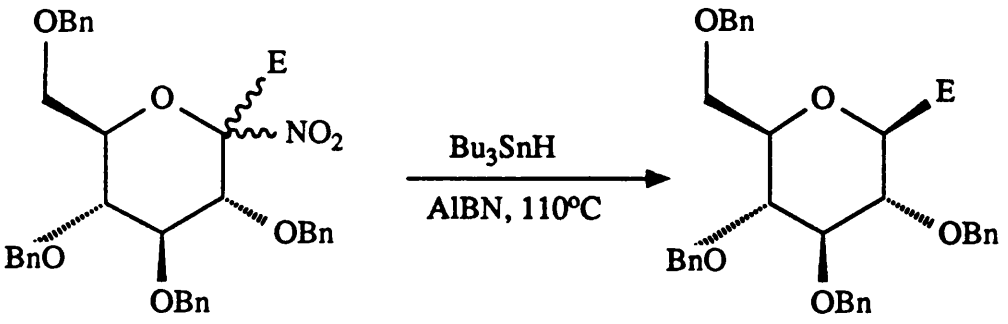
44



45

In a similar fashion, the intermediate alkylated glycosyl nitro derivative **46** can be reduced stereospecifically[64a] to give the product **47** with β-stereochemistry at the anomeric centre (Scheme 36).

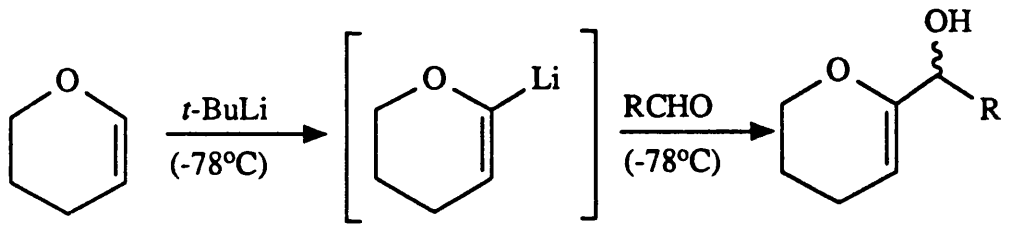
Scheme 36



46 47

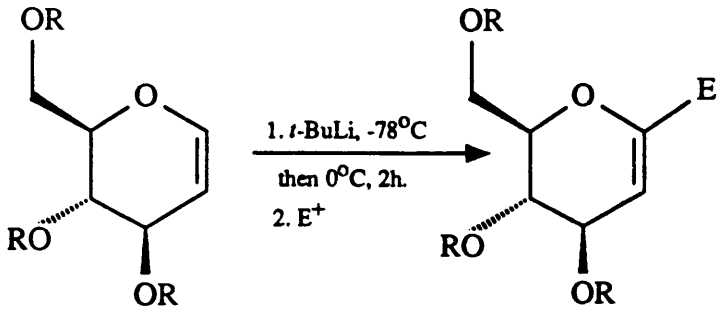
The use of heteroatom facilitated lithiation is a well established method for the formation of carbon-carbon bonds with simple dihydropyrans[77], e.g. Scheme 37.

Scheme 37



This methodology has very recently been extended to *C*-glycoside synthesis. Sinaÿ[78] has metalated the tri-*O*-*tert*-butyldimethylsilyl glucal **48** as shown in Scheme 38. Unfortunately this procedure was found to be incompatible with benzyl

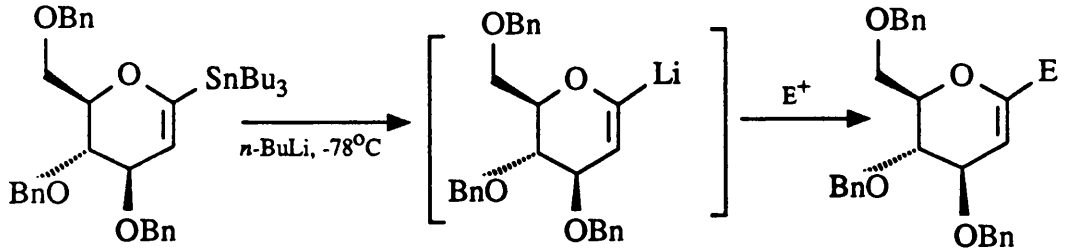
Scheme 38



R=*t*BDMS (48)
R=BN (49)

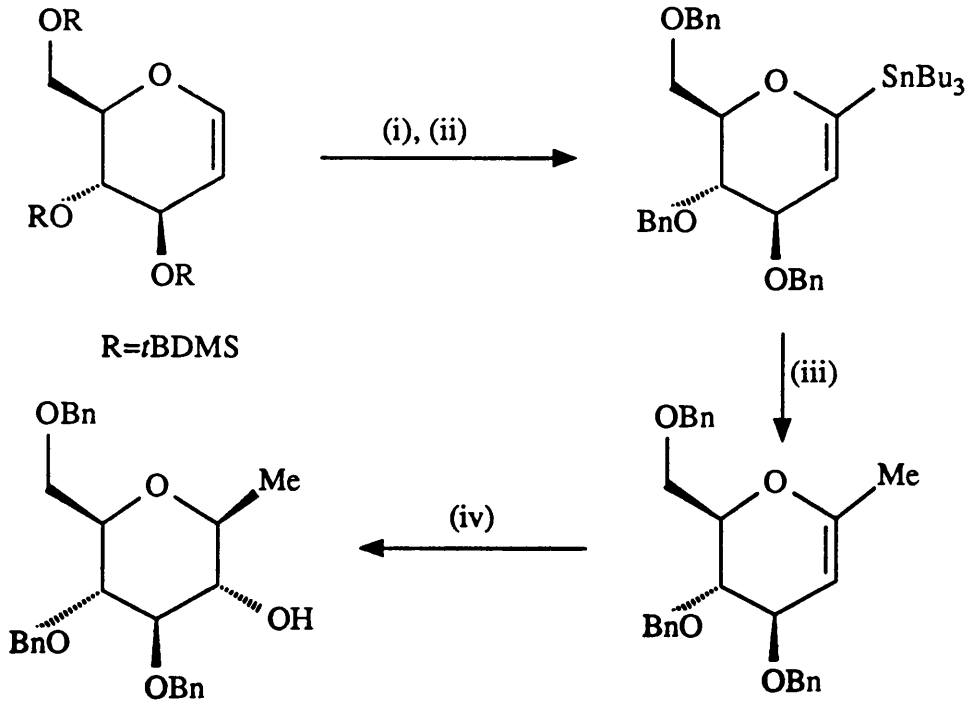
hydroxyl group protection (49). Access to lithiated 49 is available, however, from the vinyl stannane 50 using a transmetalation procedure.

Scheme 39



A similar procedure has been developed by Hanessian[79], who demonstrated that the glucal can be oxygenated stereoselectively using hydroboration technology, e.g. Scheme 40.

Scheme 40

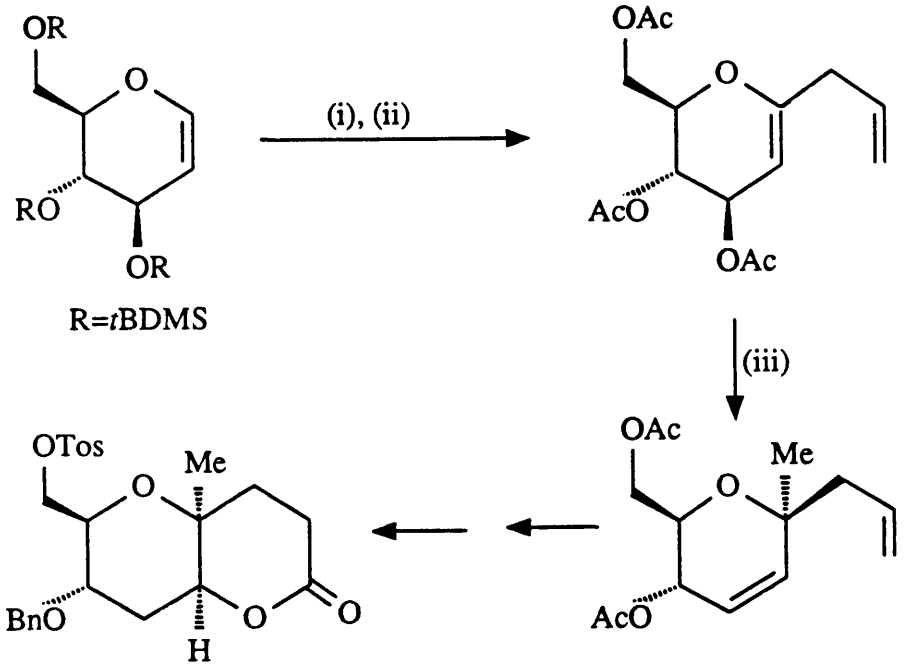


Reagents (i) *t*-BuOK, *n*-BuLi, THF, -78°C, Bu_3SnCl; (ii) TBAF then BnBr, KH, Bu_4NI, 25°C, [55%(i)+(ii)]; (iii) *n*-BuLi, THF, -78°C then MeI (88%); (iv) $BH_3.Me_2S$, NaOH, H_2O_2 (70%).

The synthetic potential of such methodology has been demonstrated by Nicolaou[80], who has used the allylation of a lithiated glycal together with a carbon-Ferrier reaction to prepare a potential building block for brevetoxin B (Scheme 41).

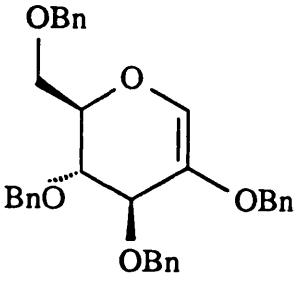
Very recently, Schmidt[81] investigated the possibility of introducing functionality at C(3) of a glycal to activate direct lithiation at C(2) via inductive and/or intramolecular complexation. Experiments with tetra-*O*-benzyl-D-glycal 51

Scheme 41

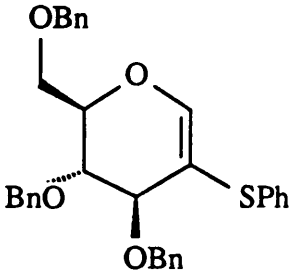


Reagents (i) *t*-BuLi (2equiv), Et_2O, -40 to 0°C, CuI (cat), CH_2=$CHCH_2Br$(75%); (ii) TBAF, Ac_2O, Py(85%); (iii) $AlMe_3$-$TiCl_4$(93%).

gave unsatisfactory results, with lithiation at the C(3)-benzyl methylene group proving to be a major problem.



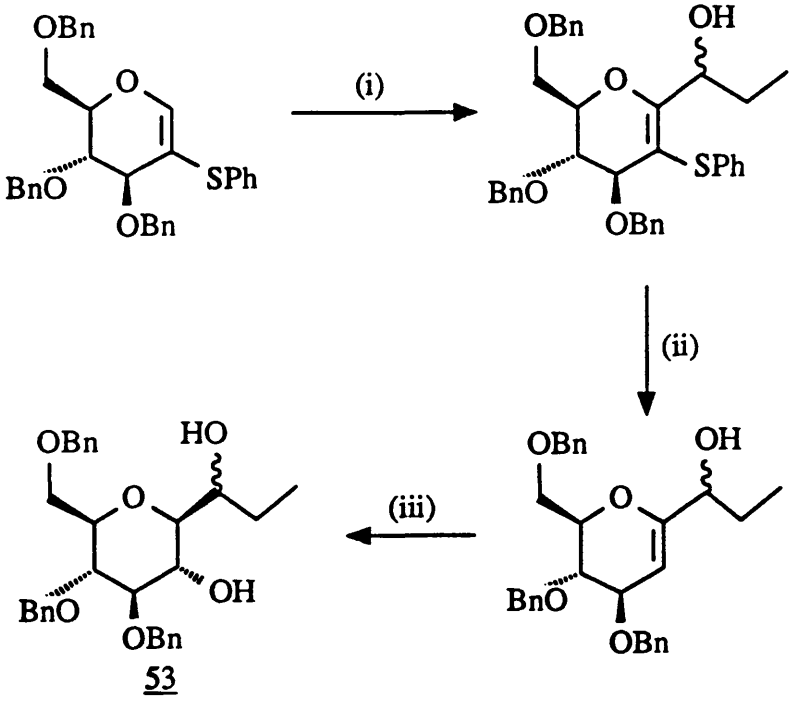
51



52

Replacement of the C(3)-*O*-benzyl group with a phenylthio moiety led to more useful reactivity. Glycal 52 can be deprotonated with lithium diisopropylamide (LDA) or *tert*-butyllithium at -78°C and then alkylated with aldehydes in good yield. Reductive cleavage of the phenylthio group followed by stereospecific introduction of a C(3)-hydroxyl function furnishes the *β*-*C*-pyranoside 53 (cf. Hanessian above, Scheme 40 and Scheme 42).

Scheme 42



53

Reagents (i) LDA or *t*-BuLi, -78°C, EtCHO (90%); (ii) Raney-Ni (quantitative); (iii) $BH_3.SMe_2$, H_2O_2, NaOH (70%).

In summary, many methods are available for stereoselectively introducing carbon-carbon bonds to the anomeric centre of tetrahydropyran rings. The pyran can react as an electrophile, a nucleophile or even as a radical. Of particular interest to this programme is the use of nucleophilic pyrans (Section 1.2).

To our knowledge, only Vassella[75] has successfully carried oxygen functionality at C(3) whilst generating an anion at C(2). For his methodology to be extrapolated to a synthesis of the herbicidins a selective oxidation of the C(3)-hydroxyl group would be required. It would be far more efficient, however, to introduce the *C*-pyranoside bond with the C(3)-carbonyl function (or an equivalent) already present.

A discussion of our attempts to synthesize *C*-pyranosides with C(3) carbonyl functionality, directed towards herbicidin synthesis, is contained in chapter 2.

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CHAPTER 1

REFERENCES (CHAPTER 1)

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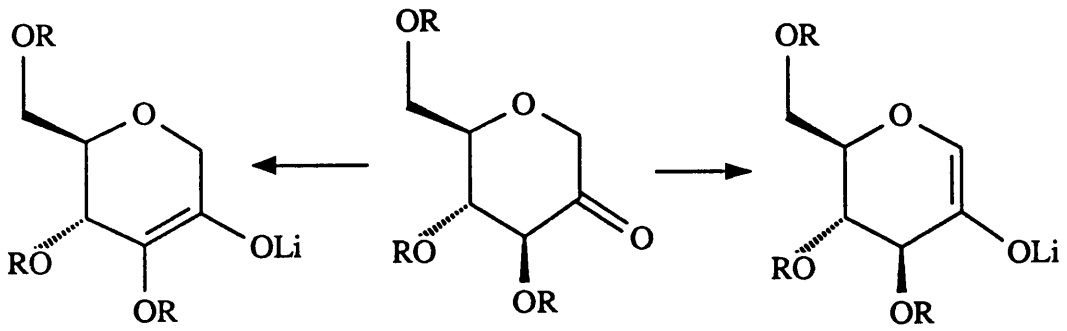
2. RESULTS AND DISCUSSION

2. RESULTS AND DISCUSSION

2.1 INTRODUCTION

In section 1.2 it was described how ketone **1** is expected to enolise away from, rather than towards the ring heteroatom, when treated with base, i.e. to give 2 rather than 3.

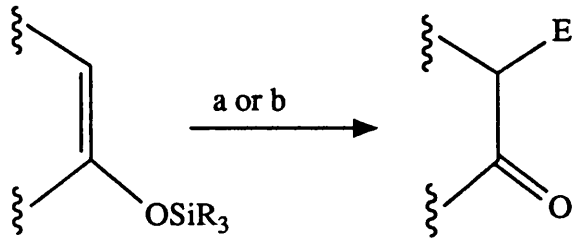


2 1 3

This mode of enolisation was not, however, compatible with our proposed synthetic approach to the herbicidin group of natural products. In order to continue with that strategy, a method of forming a carbon-carbon bond at the anomeric centre of a pyranose ring was required, where the pyran acted as a nucleophile. Any methods developed would also have to tolerate C(3)- oxygen substitution.

One possible solution to the problem was to use an enolate equivalent rather than an enolate. A commonly recognised enolate equivalent is the silyl enol ether, (e.g. **4**). This equivalence, (eq. 1), arises from two modes of reactivity:-

(i) release of the enolate using a fluoride ion[1] source such as tetra-*n*-butyl-ammonium fluoride (TBAF), and (ii) Lewis acid-mediated[2] reactions with, for example, acetals and carbonyl compounds.

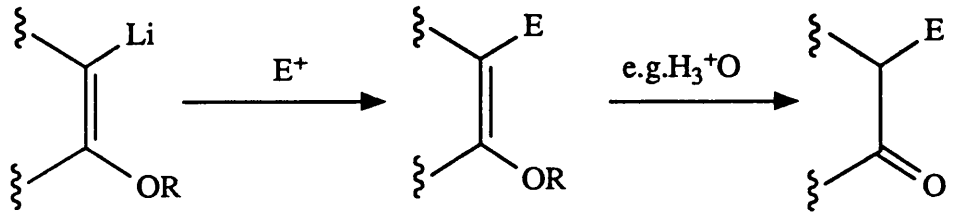


eq 1

4

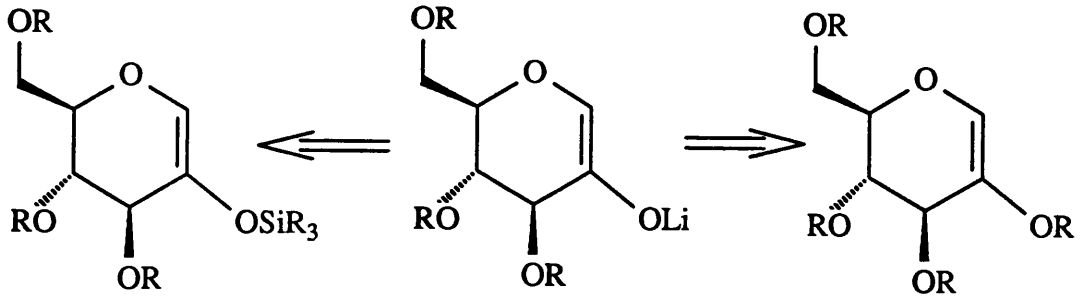
a) TBAF, E^+ ; b) Lewis acid, E^+.

An alternative but less obvious approach uses a β-lithiated enol ether, (e.g. 5), as an enolate equivalent.



5

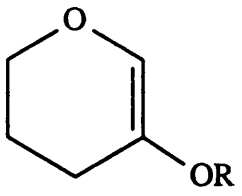
Enol ethers 6 and 7 therefore, could feasibly be used as synthetic equivalents of the regiospecific enolate 3.



6 3 7

With these strategies in mind we have undertaken model studies based on:-

1) The lithiation of 5-alkoxy-3,4-dihydro-2(*H*)-pyrans **8**.



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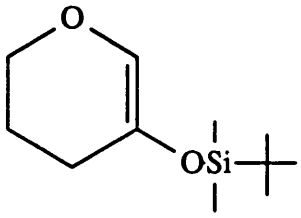
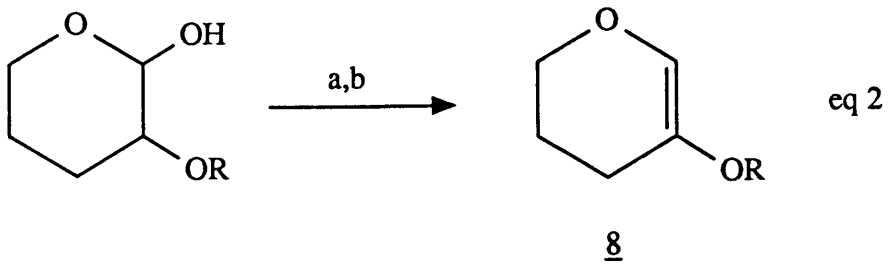
2) The Lewis acid mediated reactions of the *tert*-butyldimethylsilyloxy-3,4-dihydro-2(*H*)-pyran **9**.



9

These simple enol ethers **8** and **9** were chosen for their obvious similarity to the carbohydrate enol ethers **6** and **7**. They are also equivalents of the enolate **10**, a species which as described in section 1.2, can only be formed at a maximum of 25% yield, via direct enolisation of the ketone **12**.

To avoid direct enolisation, it was proposed that the double bond of enol ethers **8** and **9**, be introduced via the elimination reaction of equation 2.

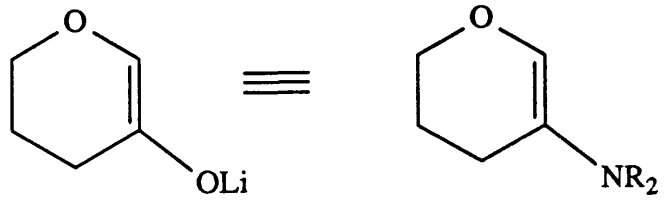


eq 2

8

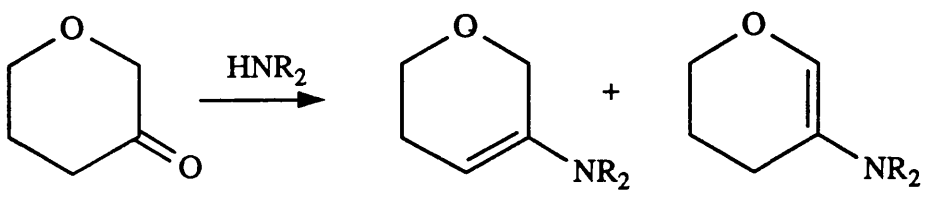
Reagents a) MsCl, NEt_3; b) reflux.

Similar elimination reactions are also available for the preparation of the carbohydrate equivalents of 8[3], allowing ready extension of the model studies to natural product synthesis.



10 11

Enamines such as 11 have been presented as equivalents of the regiospecific enolate 10[4]. However, they are prepared by condensation of a secondary amine with ketone 12 and inevitably mixtures of 11 and 13 result.



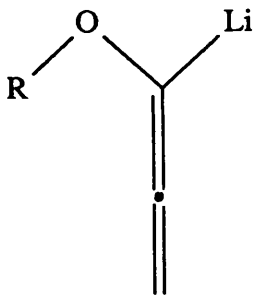
12 13 11

In summary, the enol ethers **8** and **9** were proposed as equivalents of the regiospecific enolate **10**. It was hoped that they would provide a more efficient alternative to the enamine **11**. The ultimate objective was that any methodology developed should be applicable to the synthesis of the herbicidins.

The results of our studies are reported in the remainder of this chapter.

2.2 METALATED ENOL ETHER APPROACH

It is commonly recognised that the acidity of a proton on a carbon atom increases as the hybridisation of the carbon atom changes: $sp^3 < sp^2 < sp$. The effect of the introduction of an α-heteroatom on the acidity of a proton bonded to an sp^2 hybridised carbon atom is also well documented[5]. It is not surprising, then, that α-heteroatom-facilitated metalations have found increasing utility in synthetic organic chemistry[5].



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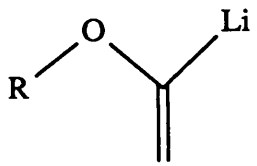

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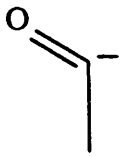
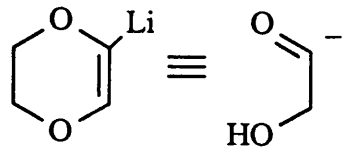


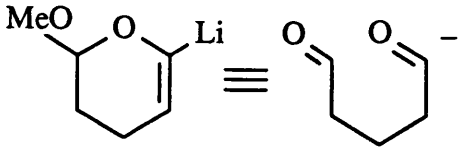
16

The first recorded example of the metalation of a vinyl ether was that of the 1-alkoxy-1-lithioallene **14**[6]. Subsequently both Schöllkopf[7] and Baldwin[8], have investigated the use of the simple alkoxyvinyl ether **15** as an acyl anion equivalent (**16**), hence highlighting the synthetic utility of such species. Since this pioneering work, the use of such anionic species has been extended to simple cyclic vinyl ethers[9]. A number of these species along with their formal synthetic equivalence is shown in Scheme 1.

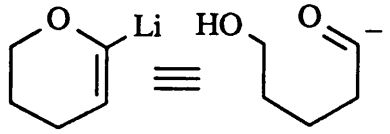
Scheme 1



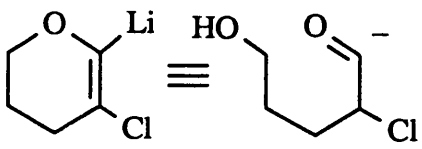
17 (ref 9b)



19 (ref 9a)



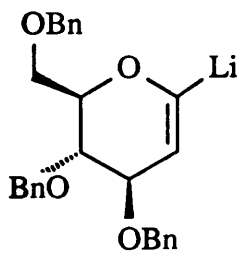
18 (ref 9a)



20 (ref 9a)

A particularly pertinent example is vinyl chloride 20 and it should be noted that the presence of the β-heteroatom enhances the kinetic acidity of the alkenyl proton[9a].

Most recently, during the course of our studies, the use of α-heteroatom facilitated lithiations has been extended still further to encompass carbohydrate derived enol ethers (or glucals) such as 21[10], 22[11] and 23[11].



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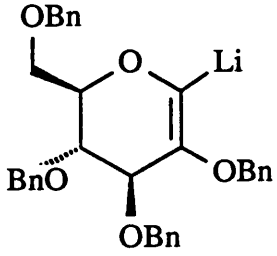

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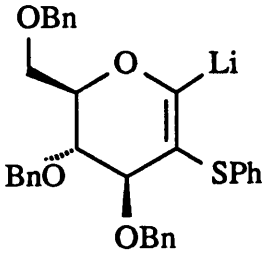
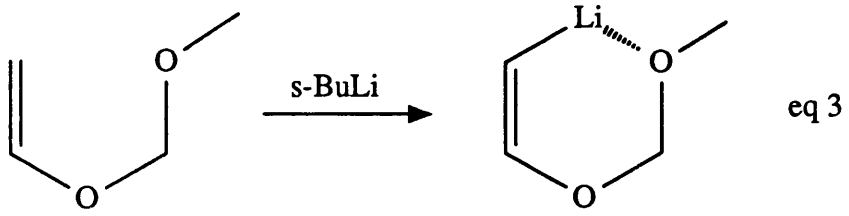


23

The two fully functionalised glucose derivatives 22 and 23 in principle provide a synthetic entry into the herbicidins. However, the lithiation procedure was shown[11] to be incompatible with the benzyl groups, in the case of 22, and the C(3) functionality of sulphide 23, has not been developed in the sense of providing access to the 3-keto derivative.

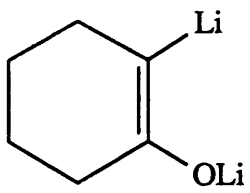
Our proposed model study involves the metalation of enol ether **8**. The success of this approach relies not only on the α-heteroatom but also on the enolate equivalence of a β-lithiated enol ether. β-Lithiated enol ethers have previously been used as enolate equivalents. However, direct deprotonation, as in eq. 3, is only possible when the oxygen protecting group is capable of co-ordinating to the metal counter ion as in **24**[12].



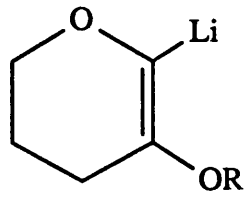
eq 3

<u>24</u>

Alternatively, β-lithiated enol ethers can be generated by halogen-metal exchange[13] or transmetalation[14], when the oxygen protecting group is non co-ordinating. A similar approach uses dianions such as **24a** as an enolate equivalent[15].



<u>24a</u>



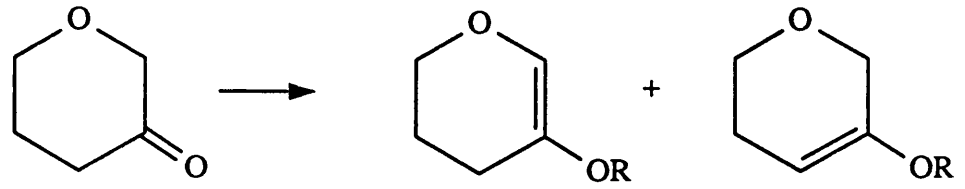
<u>25</u>

In summary, a heteroatom α- to an sp^2 hybridised carbon atom will facilitate deprotonation. The β-oxygen substituent should allow the metalated enol ether 25 to act as an enolate equivalent, whilst promoting direct lithiation at the vinylic position through inductive effects and intramolecular complexation of the lithiated species.

The objectives of the study were therefore:-

a) An efficient synthesis of a series of 5-alkoxy-3,4-dihydro-2(*H*)-pyrans.

The only methods available for the synthesis of species such as **8** involve trapping the enolate derived from ketone 12, a process which as described in section 1.2, is inefficient.



Minor Major

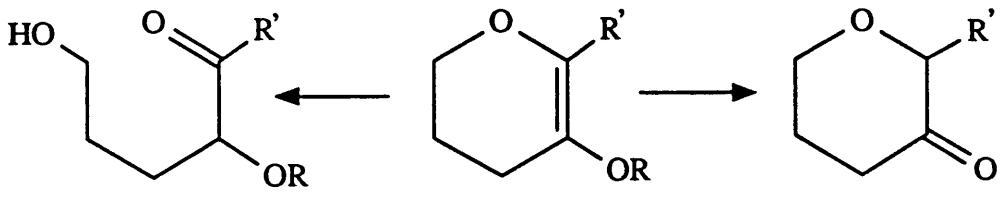
12 8

An efficient synthesis of enol ethers such as **8** was therefore developed.

b) Metalation of 5-alkoxy-3,4-dihydro-2(*H*)-pyrans.

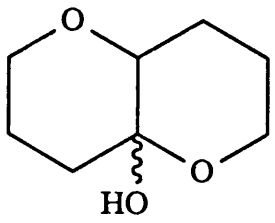
Based on literature precedent, studies were conducted on the lithiation of two enol ethers (**8**, R=Me and Bn).

c) The deprotection of the carbonyl functionality



27 26 28

Adducts such as **26** have two masked carbonyl functions. Methods have been developed for the selective deprotection of **26** to give exclusively **27** or **28** (or a functional equivalent). Included in this study is a synthesis of the bicyclic hemiketal **29** which contains the two key structural features of the herbicidins; i.e. the *C*-pyranoside linkage and hemiketal.



29

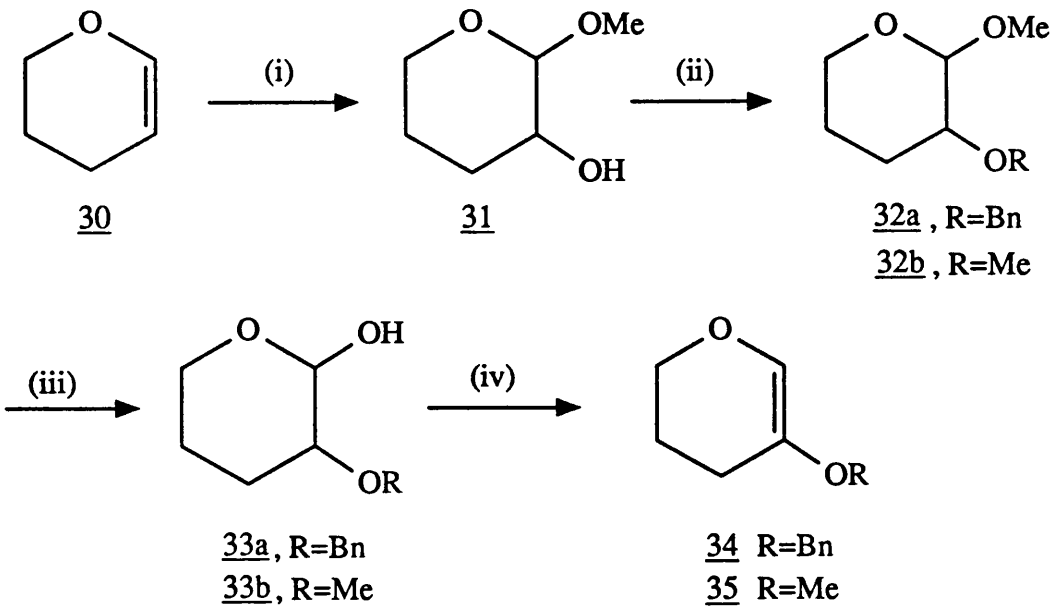
d) Reaction of metalated enol ethers (e.g. **25**) with carbohydrate electrophiles.

Although this was only a model study, we felt it necessary to evaluate the compatibility of metalated enol ethers such as **25**, with carbohydrate electrophiles suitable for herbicidin synthesis. Two such electrophiles have been investigated. The results of this preliminary investigation are also reported.

2.2a The synthesis of 5-alkoxy-3,4-dihydro-2(*H*)-pyrans

The lack of literature precedent for the synthesis of 5-alkoxy-3,4-dihydro-2(*H*)-pyrans led us to develop the route outlined in Scheme 2.

Using Brown's[16] procedure, dihydropyran **30** was treated with *meta*-chloroperoxybenzoic acid (*m*CPBA) in methanol, resulting in formation of the hydroxyacetal **31** in 85% yield. This selective protection of the anomeric hydroxyl group allowed the introduction of protecting groups at the free secondary hydroxyl, which would be stable to acid hydrolysis. The two substituents chosen were the benzyl and methyl residues. The methyl group was introduced using conditions also



Reagents (i) *m*CPBA, MeOH (85%); (ii) NaH, DME, a) BnBr (95%) or b) MeI (98%); (iii) H_3^+O, **33a** (80%), **33b** (66%); (iv) MsCl, Et_3N, 0°C then reflux, **34** (60%), **35** (75%).

established by Brown[16]; i.e. treatment of **31** with methyl iodide (MeI) and sodium hydride (NaH) in dimethoxyethane (DME) gave **32b** in 98% yield. Alkylation under the same conditions[17], but replacing MeI with benzyl bromide (BnBr) produced **32a**[18] in 95% yield. Selective deprotection of the anomeric hydroxyl group was accomplished in both cases using aqueous hydrolysis[19]; these conditions had previously been used to prepare **33b** but not **33a**[20]. In our hands the reaction afforded **33b** in 62% and **33a** in 80%.

It should be noted that **31**, **32a/b** and **33a/b** have two chiral centres. However, it was not necessary to separate the diastereoisomers, as the stereochemistry was irrelevant to this study. Ratios of isomers were not investigated and mixtures were

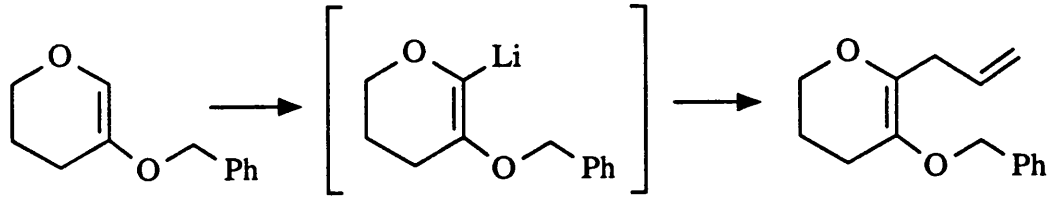
taken on after purification. For a discussion of the stereochemical implications of reaction (i), Scheme 2, the reader is referred to the work of Brown[16].

Dehydration of hemiacetals **33a** and **b** was achieved by preparing the mesylates with methanesulphonyl chloride (MsCl) and triethylamine (Et_3N) in chloroform at 0°C. When formation of the mesylates was complete, as observed by t.l.c., the mixtures were heated at reflux to give the benzyloxy-3,4-dihydro-2(*H*)-pyran (**34**) in 60% yield and methoxy-3,4-dihydro-2(*H*)-pyran (**35**) in 75% yield respectively.

It proved difficult to monitor formation of the intermediate mesylates as they were susceptible to hydrolysis even on t.l.c.. This problem was circumvented by quenching t.l.c. samples of the reaction mixtures with methanol. Any mesylate present in such samples reacted to give the corresponding methoxy acetal **32a/b**. Formation of the mesylate was then followed by formation of the acetals **32a/b** by t.l.c.

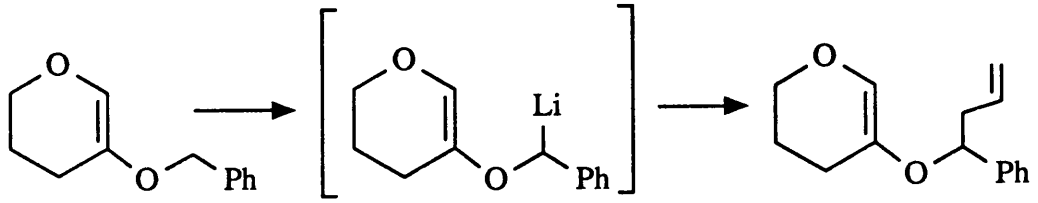
2.2b Metalation of 5-alkoxy-3,4-dihydro-2(*H*)-pyrans

Based on the conditions developed by Boeckman[9a], enol ether **34** was treated with *tert*-butyllithium in tetrahydrofuran (THF) at -78°C and then the solution was warmed to 0°C for 0.5h to promote complete lithiation. The resulting solution was then re-cooled to -78°C before allyl bromide was added in an attempt to trap the lithiated enol ether intermediate **36**. Although a new product was isolated from



34 36 37

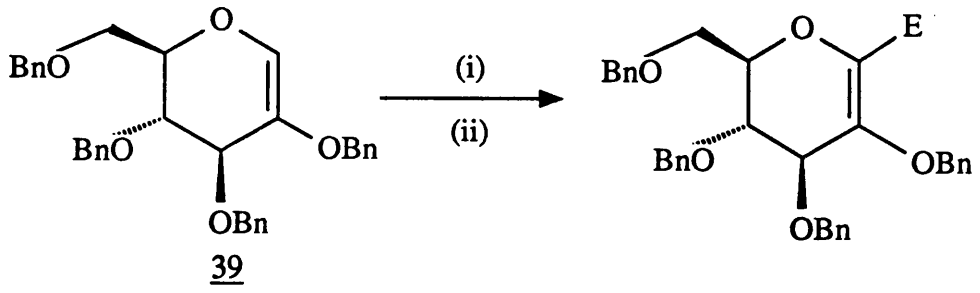
the reaction in 50% yield after purification, it was clearly not the desired alkylated product **37** as indicated by the presence of the vinylic proton at δ 6.1, t, J = 1.5 Hz [cf. **34**, δ 6.3 (t, J = 1.5Hz)] in the 270 MHz ^{1}H n.m.r. spectrum. Further examination of this spectrum combined with the other spectral data led to the conclusion that the product was one derived from benzylic deprotonation and subsequent alkylation; i.e. **38**.



34 38

A second attempt at the vinylic deprotonation involved treatment of enol ether **34** with *tert*-butyllithium at -78°C in THF for 0.25h followed by addition of allyl bromide. However, this lower temperature still resulted in benzylic deprotonation and trapping to give product **38** in 56% yield. It was not clear whether kinetic deprotonation was occurring at the benzylic position of enol ether **34**. However, this aspect has not been pursued.

Recently, Schmidt[11] has reported that deprotonation of 1-benzyloxy-3,4,6-tri-*O*-benzyl-D-glucal(**39**) is possible at the vinylic position though competing lithiation at the benzyl methylene groups, mainly *C*(3) was a severe problem.

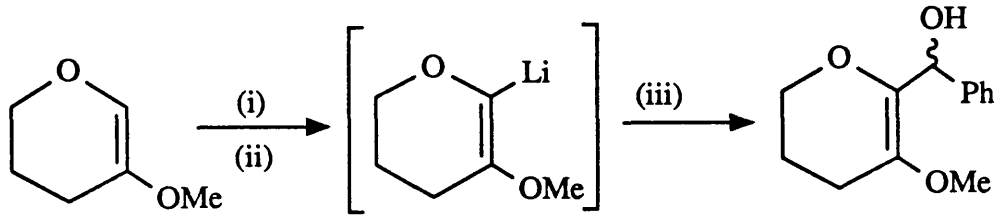


39

Reagents (i) *n*-BuLi, *t*-BuOK, THF, -100°C; (ii) Electrophile, E^+; e.g. $(MeS)_2$, MeI, $ClCO_2Me$.

No such complications were observed with the methyl enol ether **35**. Addition of *tert*-butyllithium to methyl enol ether **35** at -78°C in THF followed by warming of the solution to 0°C and stirring for 0.5h effected lithiation. After re-cooling to -78°C, addition of benzaldehyde to the solution of anion **41**, resulted in formation of adduct **40** in 61% yield after purification. In order to optimize the conditions for the lithiation of enol ether **35**, the use of alternative ethereal and hydrocarbon solvents was examined along with variation in the temperature at which lithiation was conducted (i.e. X, Scheme 3 and Table 1).

Scheme 3



35 41 40

Reagents (i) Base, -78°C; (ii) warm to X°C for T h; (iii) cool to -78°C, add benzaldehyde.

Table 1

Entry	Base	Solvent	Temp(X)°C	Time (T)h	Yield 40(%)
1	*t*-BuLi	THF	-78°C	0.5	0
2	*t*-BuLi	THF	-40°C	0.5	51
3	*t*-BuLi	THF	0°C	0.5	61
4	*t*-BuLi	Ether	0°C	0.5	60
5	*t*-BuLi	Petrol	0°C	0.5	33
6	*t*-BuLi	DME	0°C	0.5	16
7	*n*-BuLi	THF	50°C	1	61
8	*n*-BuLi	THF	19°C	2	67

The reaction outlined in Scheme 3 was used to monitor the efficiency of the metalation and the results are displayed in Table 1. Contrary to Boeckman's observations[9a], it was found that lithiation occurred in petroleum ether (b.p. 30-40°C) giving **40** in 33% yield after purification. In diethyl ether the yield of 40 was comparable to that found in THF. Boeckman found that 3,4-dihydro-2(*H*)-pyran was metalated in less than 5% yield in diethyl ether, *n*-pentane and DME.

The enhanced reactivity of methyl enol ether **35** over 3,4-dihydro-2(*H*)-pyran is presumably a consequence of the oxygen substituent. This could be participating in the disruption of the aggregate structure of *tert*-butyllithium[21]. Alternatively the inductive effect of the oxygen may increase the acidity of the vinyl proton. A third explanation is that the oxygen atom could participate in intramolecular complexation of the lithiated species **41**, resulting in increased stabilisation. The most probable explanation is that all three effects contribute to the enhanced reactivity of **35**.

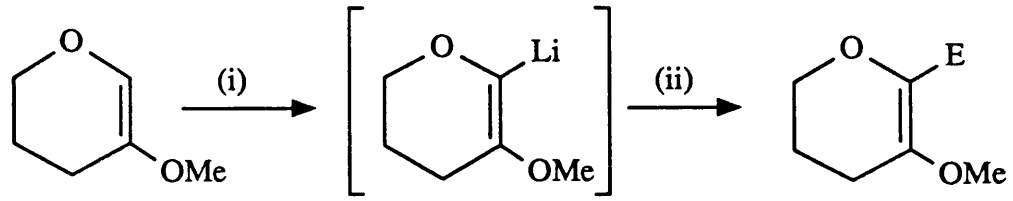
The use of *n*-butyllithium as base at higher temperatures was also investigated using the procedures outlined by Amaroux[22] as precedent (entries 7 and 8 Table 1). These procedures were found to be as efficient as those in which *tert*-butyllithium had been used and procedures 3 and 7 (Table 1) were eventually adopted as the methods of choice for lithiation of **35**.

Having established the best conditions for lithiation, a crude guide to the reactivity of anion **41** was obtained by investigating its reactions with a number of other electrophiles. The results of this study are shown in Table 2.

We found that the carbonyl-based electrophiles, such as entries 1, 2 and 3 in Table 2, reacted rapidly with **41** at -78°C. Primary alkyl halides, such as **42** and **44**, did not react with anion **41** at -78°C and required warming to 50°C for 1h before reaction was complete.

The iodides **42**[23,24] and **44**[25,26] were both prepared from 3-bromo-1-propanol **46** as outlined in Scheme 5.

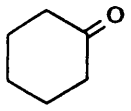
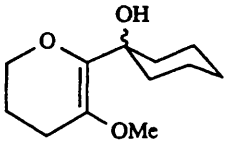
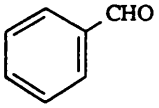
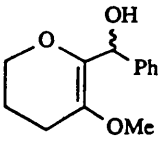
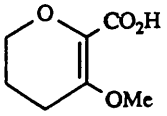
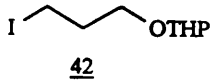
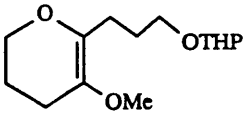
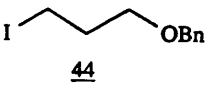
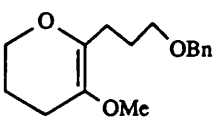
Scheme 4



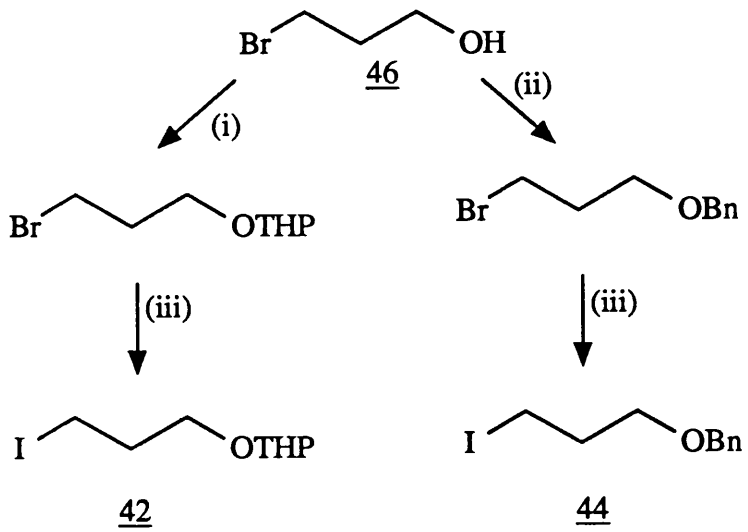
35 41

Reagents (i) see Table 1 entries 3 or 7; (i) Electrophile E^+.

Table 2

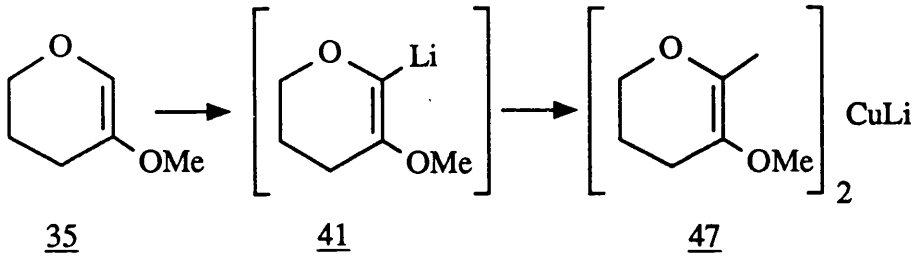
Entry	Metalation Procedure (i)	Electrophile	Adduct	Yield
1	3			53%
2	3			61%
3	3	CO_2		47%
4	7	 42	 43	54%
5	7	 44	 45	65%

Scheme 5



Reagents (i) $POCl_3$, dihydropyran (62%); (ii) NaH, BnBr (48%); (iii) NaI, acetone 42 (80%), 44 (83%).

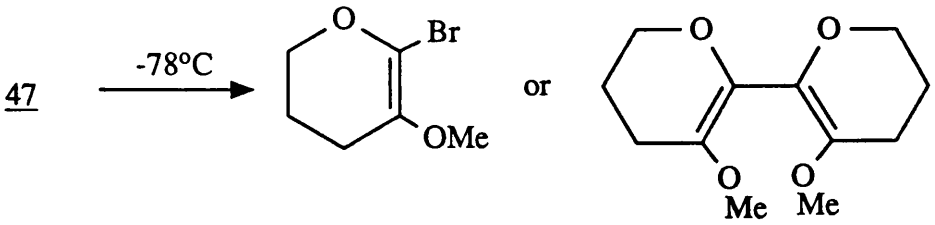
In an attempt to extend the synthetic utility of anion **41** the use of the homocuprate derivative **47** was investigated.



Preparation of **41** using *tert*-butyllithium in THF (Table 1, entry 3) was followed by conversion to the homocuprate **47** by treatment with cuprous iodide (CuI) in THF at -78°C[27]. An attempt was made to react this species with benzyl bromide and a product was isolated which was strongly u.v. active on t.l.c.. The ^1H n.m.r. spectrum indicated that a reaction had occurred at the vinylic position (no

proton resonance was observed at ~ δ 6.0). However, it was also apparent that the benzyl group had not been incorporated. The lability of this product precluded any further characterisation but it was possible to postulate from the limited spectral data available, that it could have been one of two products; either **48**, the product of halogen-metal exchange, or **49**, the product of dimerisation of cuprate **47**.

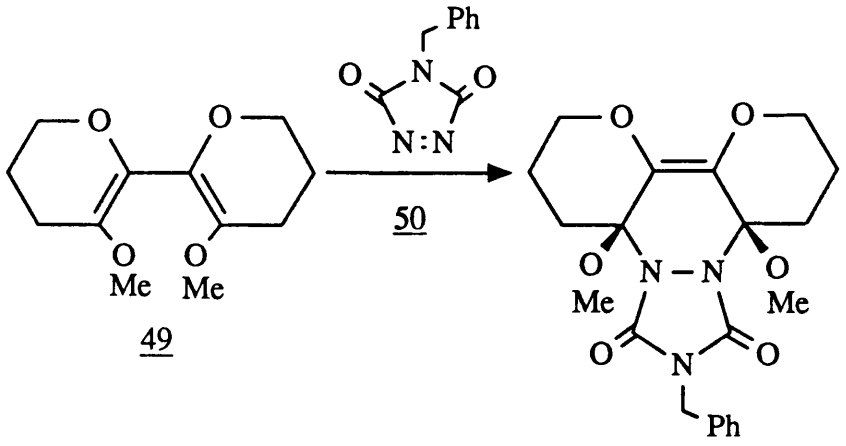
Scheme 6



48 49

During a second attempt to prepare and trap the homocuprate **47**, the lithiated enol ether **41**, generated as described above, was transferred to a suspension of CuI in THF at -78°C to give a dark green/black suspension. Analysis (t.l.c.) of this suspension after 0.75h at -78°C indicated that the same unknown compound observed in the benzyl bromide reaction, had already formed in significant amounts. This observation precluded **48** as a possible product of the reaction in Scheme 6. Allyl bromide was added at this stage in an attempt to trap any remaining homocuprate and the mixture was allowed to warm to room temperature. After stirring overnight at room temperature the composition of the reaction mixture had not changed.

Assignment of the product of the cuprate reaction, as the labile diene **49**, was based on its Diels Alder reaction with *N*-phenyltriazolinedione **50** at 0°C. The cycloadduct **51** was produced as a crystalline solid in 54% yield for two steps; i.e. formation of dimer and Diels Alder reaction.



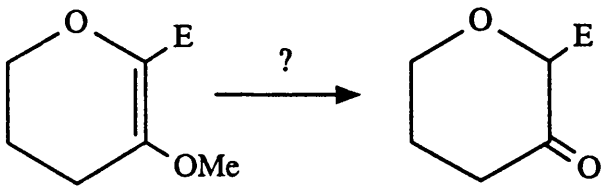
49 50 51

At this stage we have been unable to generate and react the homocuprate of the lithiated methyl enol ether **41**, using the same conditions developed by Kocienski[27] for the preparation and reaction of the homocuprate of 3,4-dihydro-2(*H*)-pyran. There are other methods of generating cuprate reagents but these have not been investigated.

2.2c Deprotection of the masked carbonyl functions

If this metalated enol ether approach was to be a successful one within the context of a regiospecific enolate equivalent, then a method of selectively deprotecting the masked carbonyl functionality was required, as shown in Scheme 7.

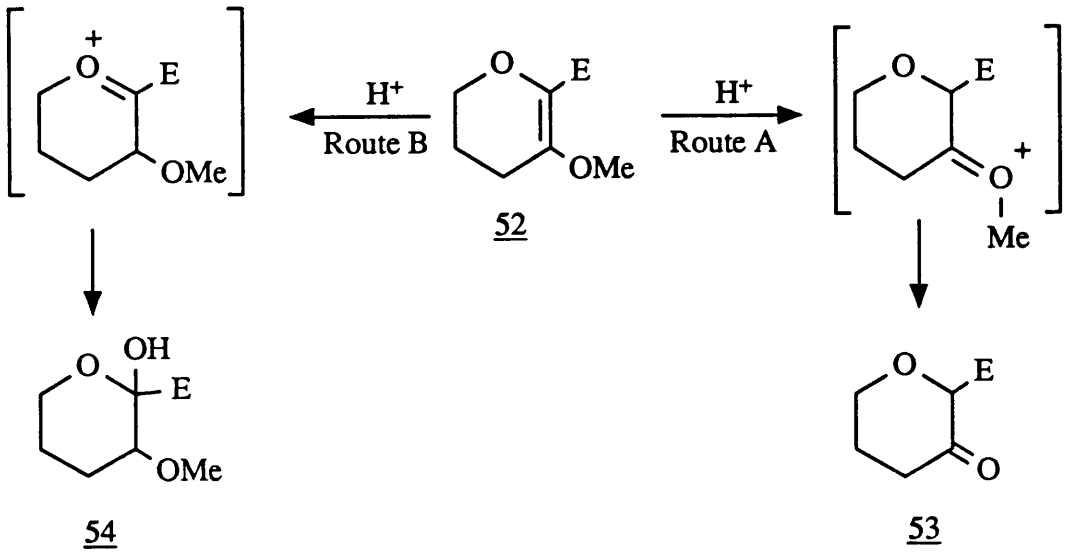
Scheme 7



52 53

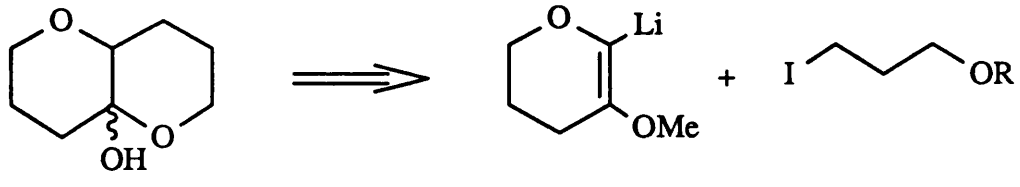
A commonly used method for achieving this transformation is aqueous hydrolysis of the enol ether moiety. However the adduct **52** contains two enol ether functions which can, in principle, undergo competitive hydrolysis under these conditions as shown in Scheme 8.

Scheme 8



52 54 53

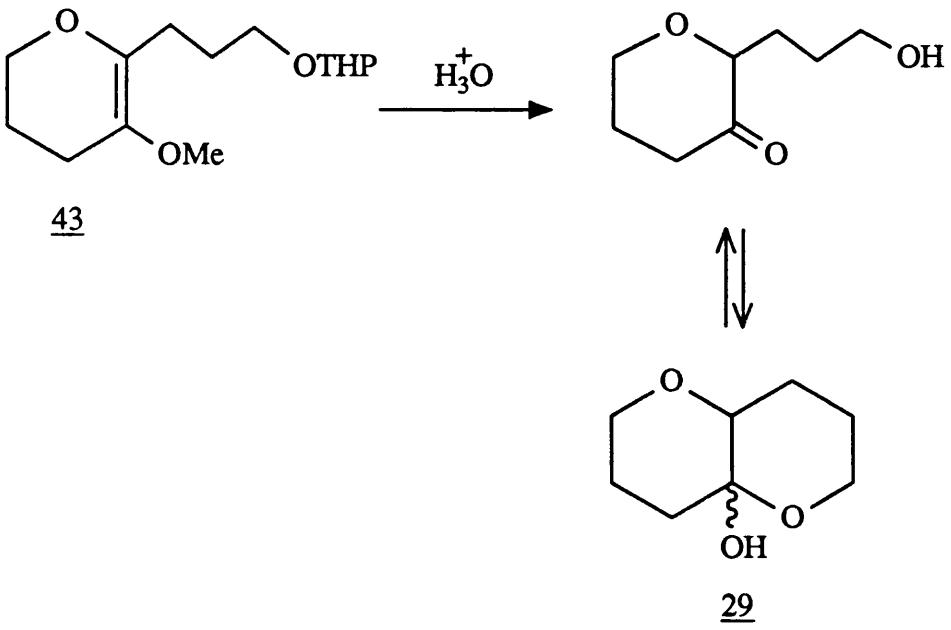
Aqueous hydrolysis of adducts such as **52** might then be expected to give mixtures of products **53** and **54**, the ratios of which will be controlled by the carbocation-stabilising ability of the substituent E. This problem must be tackled in order to achieve a synthesis of the bicyclic hemiketal **29**, which contains the two key structural features present in the herbicidin group of natural products, i.e. the *C*-pyranoside bond and the hemiketal group.



29 41 55

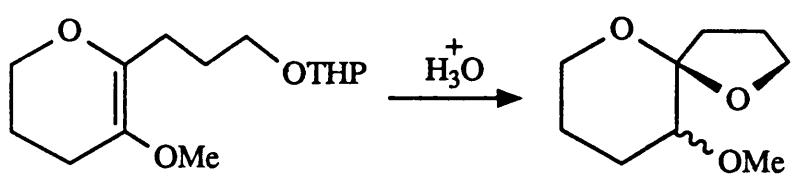
We described in section 2.2b how the key carbon-carbon bond can be introduced. In order to construct hemiketal 29 an electrophile incorporating a three-carbon unit with a protected primary hydroxyl functionality such as 55 was required. Two such electrophiles were prepared (R = Bn 44, and R = THP 42) as depicted in Scheme 5 and the adducts 45 and 43 have been described in Table 2 (entries 4 and 5).

The most obvious route to 29 is via hydrolysis of the tetrahydropyranyl (THP) protected adduct 43, as both the THP and enol ether functions are acid labile.



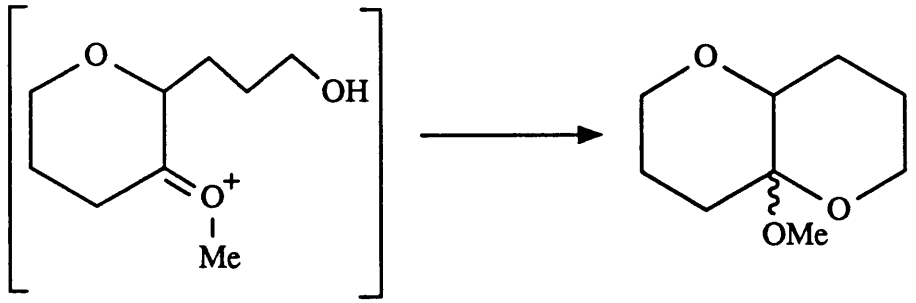
43 29

However, hydrolysis of the enol ether could occur via the alternative mechanism (route B, Scheme 8) to give the spiroketal 56[28].



43 56

It is also conceivable that under the reaction conditions the oxonium intermediate **57** could be intercepted to give the methylketal **58**, although this species would be expected to undergo facile hydrolysis to give **29**.



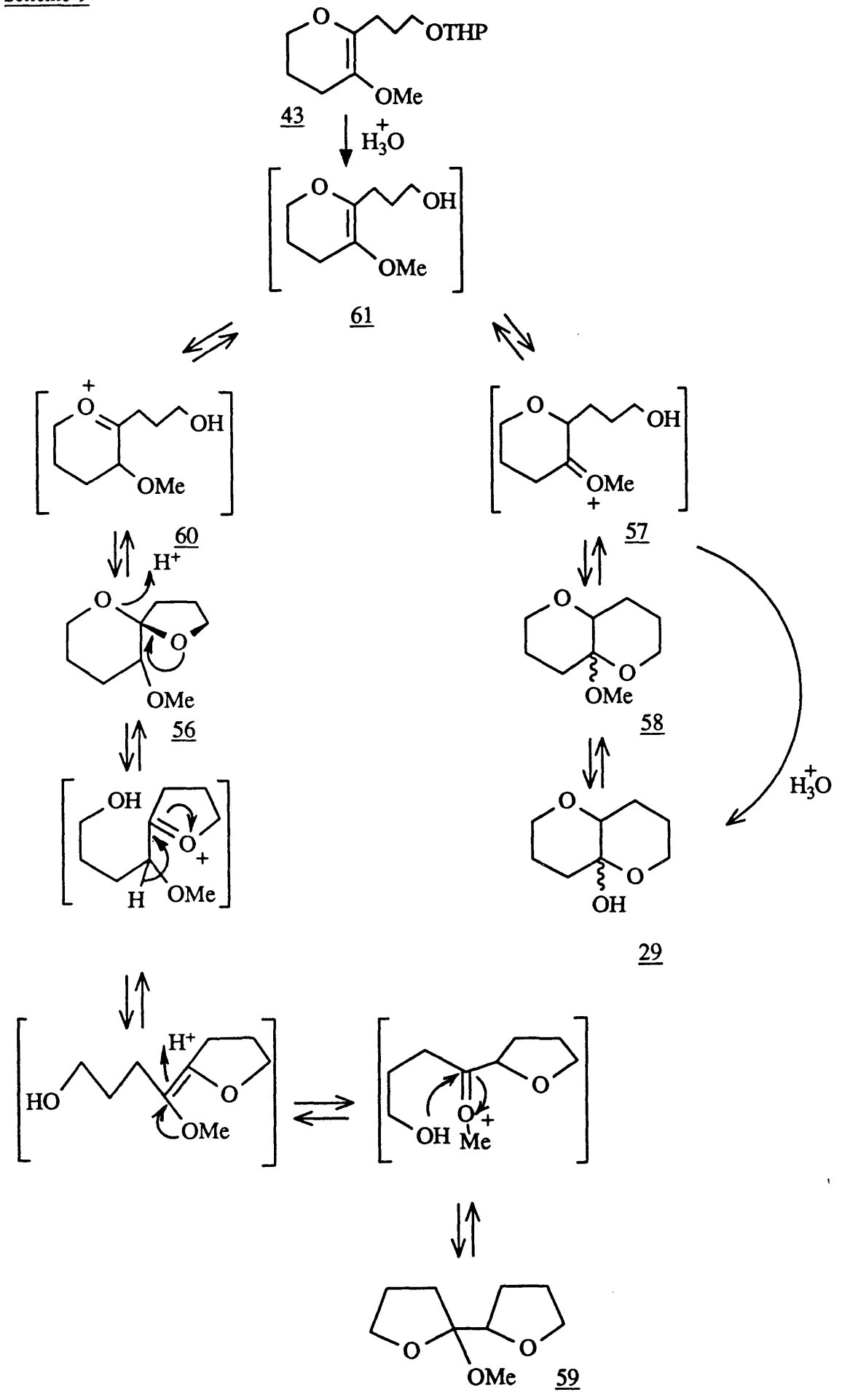
57 **58**

A third possibility is that under the acidic conditions the spiroacetal **56** could rearrange to give the bis-furan **59** as outlined in Scheme 9.

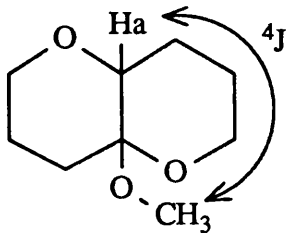
All of the possible products along with what are considered to be the more important intermediates are shown in Scheme 9. It is assumed that the THP group will be cleaved first (experimental evidence will be presented to support this assumption), although the order in which hydrolysis occurs should not alter the reaction products.

When adduct **43** was allowed to stand in concentrated hydrochloric acid (HCl)-water-THF (1:5:20) solution[27] for 12h a 1:1 mixture of two products resulted and separation of these compounds, on a preparative scale, was possible using radial chromatography. From the 270MHz ^{1}H n.m.r. spectra it was apparent that both compounds contained methoxyl groups (δ 3.38 and δ 3.37 respectively). Bicyclic hemiketal **29** is therefore excluded as either of the two products. The similarity in the spectral details of the two compounds, i.e. ^{1}H n.m.r., i.r., mass spectrum and high resolution accurate mass data, suggested that reaction had yielded a diastereomeric mixture of one of **56**, **58** or **59**. Scrutiny of these three structures shows that each system has 1 methyl, 6 methylene, 1 methine and 1 quarternary carbon centres bearing similar electron withdrawing substituents (e.g. quarternary

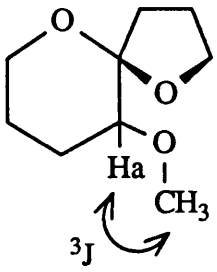
Scheme 9


OTHP
OMe
43
H_3O^+
OH
OMe
61
OH
OMe
60
H^+
OMe
56
OH
H
OMe
OH
OMe
57
OMe
58
H_3O^+
OH
29
H^+
HO
OMe
OH
Me
OMe
59

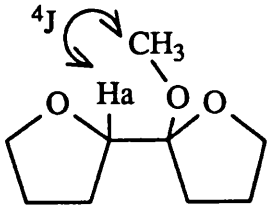
centres in **56**, **58** and **59** are directly bound to two oxygen substituents, a methylene and a methine carbon). This equivalence in the carbon skeleton prohibited unequivocal identification of the products based on standard spectroscopic evidence. N.O.e experiments also gave inconclusive results.



58



56



59

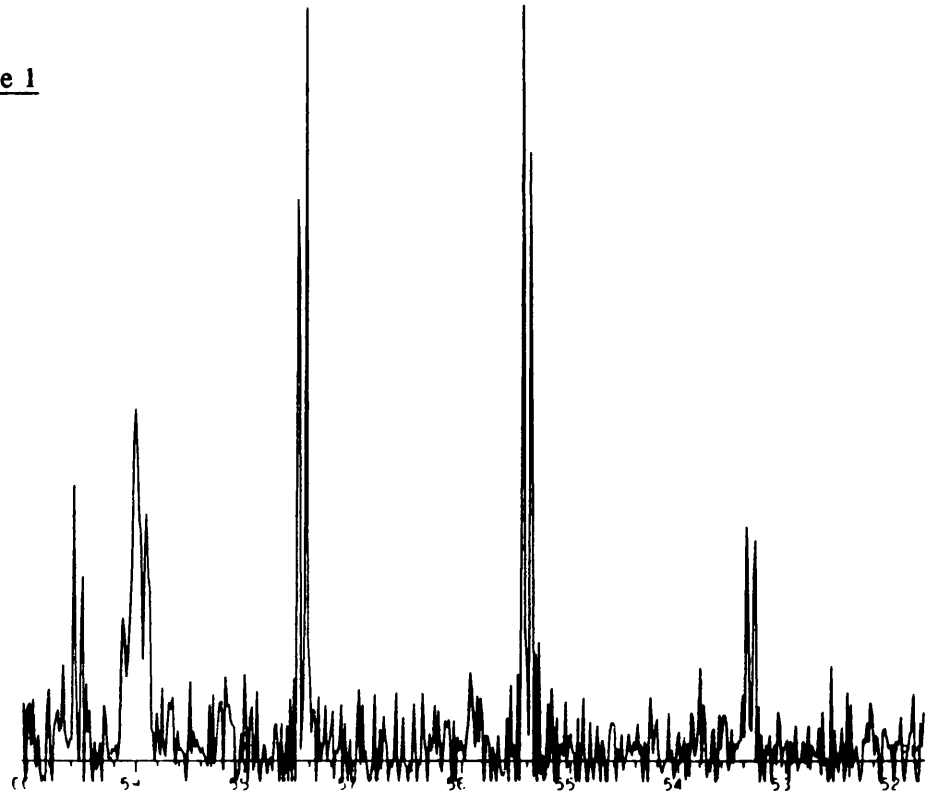
Closer examination of the three structures **58**, **56** and **59** revealed that the methoxyl group of the spiroketal **56** is bound to a methine carbon. As a result there is a three bond or ^{3}J coupling from the methine proton Ha, through the methine carbon and oxygen heteroatom to the carbon of the methyl group. Literature precedent[29] suggests that such ^{3}J couplings through oxygen, range from 3 to 7Hz.

The methoxyl group of compounds **58** and **59** are bound to quarternary carbon atoms, consequently, there is a four bond or ^{4}J relationship between the methine protons Ha and the carbons of the methyl groups. Literature precedent[29] suggests that such ^{4}J couplings through oxygen will be <1Hz if indeed a coupling is observable.

A ^{13}C n.m.r. experiment with full proton coupling would therefore enable discrimination between the spiroketal **56** and compounds **58** and **59**.

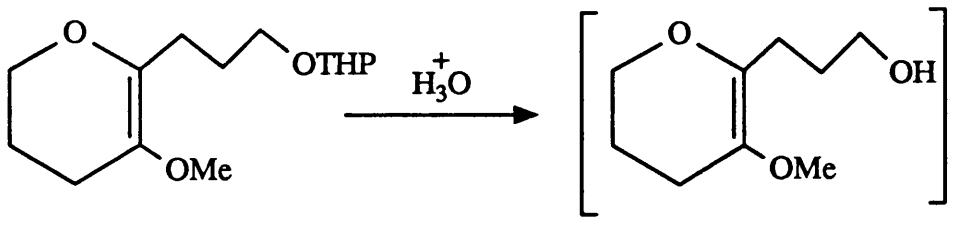
The multiplet produced by the carbon of the methyl (OMe) group of one of the products of hydrolysis of **43** is shown in Figure 1 (the second product gave a similar result δ 56.9, ^{1}J = 140Hz, ^{3}J = 4.5Hz). The quartet, δ 56.4, J = 140Hz, is due to coupling of the protons directly attached to the carbon and the doublet,

Figure 1



J=5.5Hz, is due to coupling of a methine proton. These coupling constants are consistent with the spiroketal **56**, as the product of hydrolysis of the adduct **43**.

When the hydrolysis was monitored closely it was possible to observe the formation of an intermediate. This intermediate began to form after about 10-15 min, was more polar than the starting material, slightly u.v. active and particularly sensitive when potassium permanganate solution was used to develop t.l.c. plates. It was not possible to isolate this labile intermediate but we have tentatively assigned it as the deprotected primary alcohol **61**.

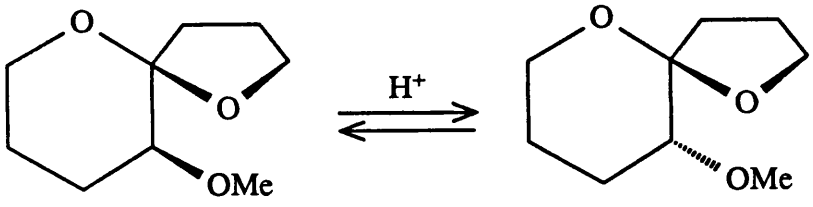


43 61

After removal of the THP group the enol ether must protonate to give the endocyclic oxonium ion **60** (Scheme 9) in preference to the exocyclic oxonium ion **57**. The spiroketals **56** must be the thermodynamically most stable products, as hydrolysis was conducted under equilibrating conditions (see later).

It was also found that when enol ether **43** was treated with *para*-toluenesulphonic acid in methanol the product was a 1:1 mixture of spiroketals **56a/b**. However, the combined yield of the two isomers was improved from 60%, (H_3^+O), to 98%. This increase in yield was attributed to the ease with which the product could be recovered from the methanol solution.

Furthermore, when the diastereomerically pure spiroketal **56a** was treated with *para*-toluenesulphonic acid in methanol at room temperature, a 1:1 equilibrium mixture of **56a** and **56b** was again formed. The same equilibrium mixture also resulted starting from diastereomerically pure spiroketal **56b**.



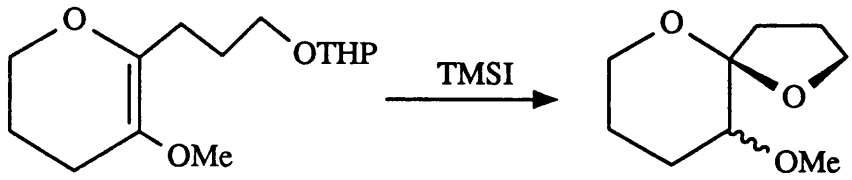
56a 56b

Although separation of the two diastereomers **56a/b** was achieved, assignment of their relative configuration was not possible owing to overlapping signals in the 400MHz, ^1H n.m.r. spectra. This precluded measurement of coupling constants and limited the value of n.O.e. experiments.

Having established that treating **43** with acid gave exclusively the spiroketals **56a/b**, an alternative method had to be found to release the carbonyl function and liberate **29**. The use of iodotrimethylsilane (TMSI) is well established for the cleavage of ether-protecting groups[30]. More recently, the use of this reagent has

been extended to the cleavage of methyl enol ethers to give carbonyl compounds[31]. As this was a mechanistically different approach, it was decided to investigate the use of TMSI as a solution to this problem.

When treated with TMSI, generated in situ from chlorotrimethylsilane and sodium iodide in acetonitrile, adduct **43** gave a 1:1 mixture of spiroketals **56a/b** in 40% yield.



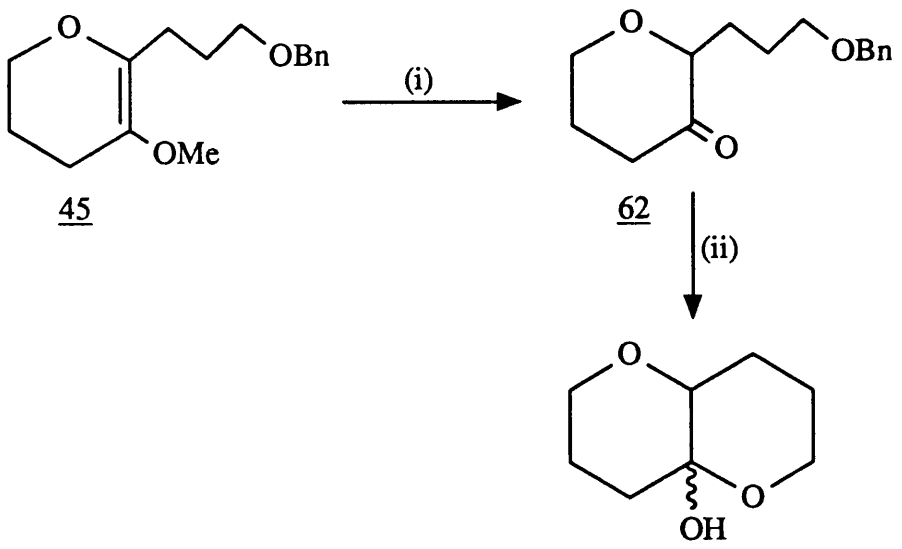
43 56a/b

The THP group contains an acetal moiety and might, therefore, be expected to be labile to treatment with TMSI, resulting in formation of **61** (Scheme 9) and as a consequence during work up, the spiroketals **56a/b**.

To avoid any possibility of forming **61** it was decided to try the reaction on an adduct in which the hydroxyl group was protected as an ether. The benzyl ether was chosen as literature precedent suggests its cleavage with TMSI is slower than a methyl enol ether[30,31]. The benzyl ether can also be cleaved conveniently using catalytic hydrogenolysis[30]. Adduct **45** was therefore prepared as outlined in Scheme 4 (Table 2, entry 5). Treatment of **45** with chlorotrimethylsilane and sodium iodide in acetonitrile, resulted in formation of the ketone **62** in 70% yield after purification.

The ketone **62** was difficult to purify rigorously and was therefore characterised as its corresponding 2,4-dinitrophenylhydrazone[32]. The crystalline derivative provided satisfactory elemental and spectroscopic data.

Scheme 10



45 62 29

Reagents (i) Me_3SiCl, NaI, acetonitrile (70%); (ii) H_2, 10% Pd/C (93%).

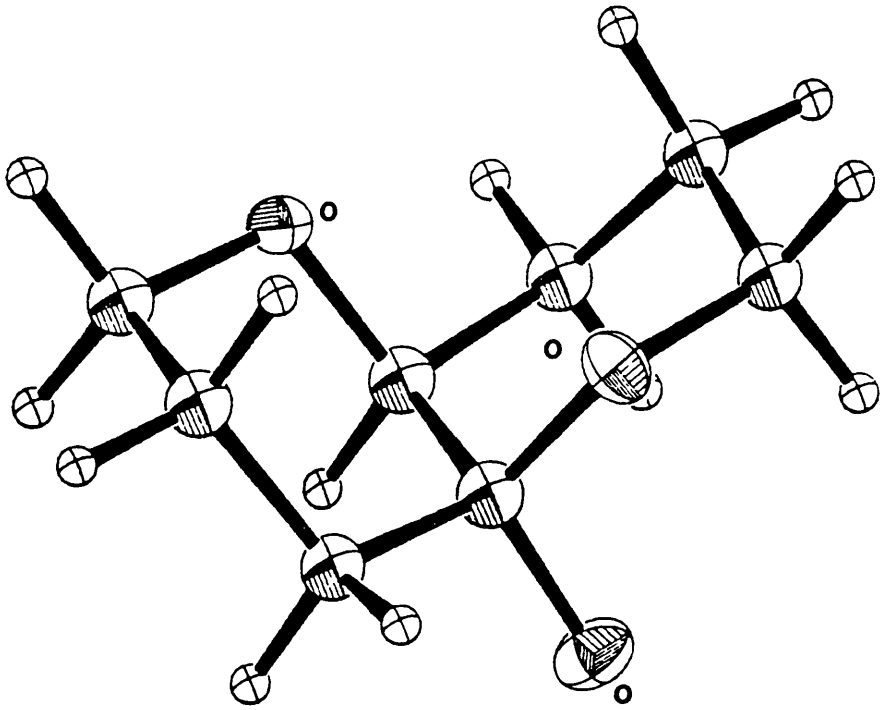
The preparation of ketone **62** represents the successful use of the metalated enol ether **41** as a regiospecific enolate equivalent.

To complete the model study, and realise our initial aim, the benzyl group of **62** was removed via catalytic hydrogenolysis to give the bicyclic hemiketal **29** in 93% yield, Scheme 10.

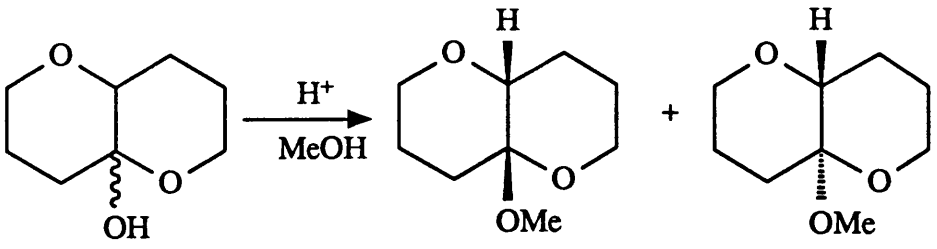
Hemiketal **29** was initially obtained as a clear colourless oil which gradually crystallised on standing at room temperature. In solution it existed as a 2:1 mixture of *cis:trans* isomers as indicated by n.m.r. studies. When **29** was recrystallised from a diethyl ether/petrol (b.p. 30-40°C) mixture, rhombohedral crystals (m.p. 78-80°C) were formed which were suitable for X-ray crystalographic studies. The ORTEP diagram resulting from a single crystal X-ray diffraction experiment is shown in Figure 2. This would suggest that in the solid state hemiketal **29** exists in the *cis*

conformation, although it is conceivable that the *cis* and *trans* isomers crystallise separately.

Figure 2



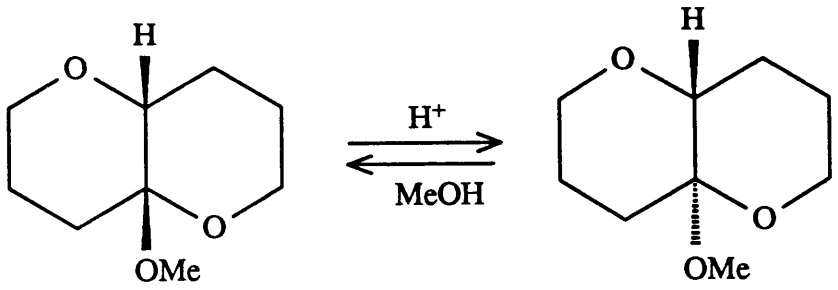
When exposed to acidic methanol at room temperature, **29** gave a 1:1 mixture of the *cis* **58a** and *trans* **58b** bicyclic methylketals in 98% combined yield.



29 58a 58b

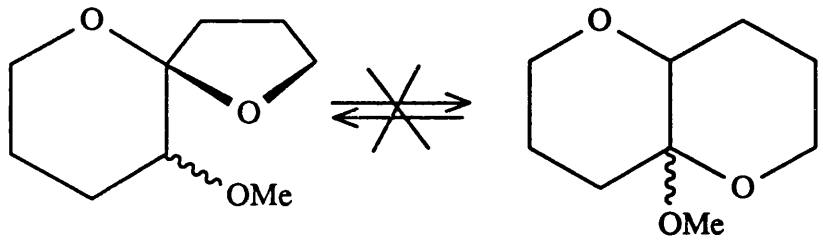
Unlike the hemiketal 29 whose *cis* and *trans* isomers rapidly equilibrated on chromatography, it was possible to separate **58a** and **58b** chromatographically and these isomers have been characterised individually.

When pure **58a** was treated with acid in methanol at room temperature, a 1:1 equilibrium mixture of **58a** and **58b** was again formed. The same result was obtained starting from pure **58b**.



58a 58b

Although in principle a mechanism is available for the interconversion of the spiroketal system **56**, and the bicyclic methylketal system **58**, e.g. Scheme 9, this conversion could not be achieved when either diastereomer was heated at reflux in acidic methanol for 5h.

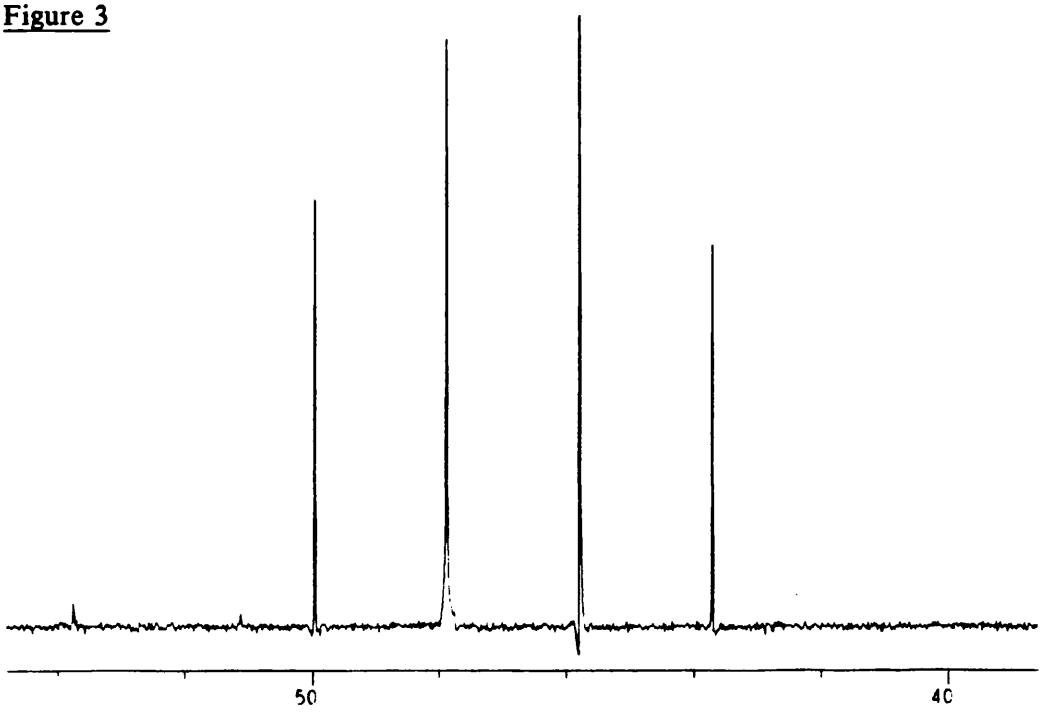


56 58

The results of these equilibration studies suggest that hydrolysis of the adduct enol ether **43** does not result in an equilibrium mixture of oxonium species **60** and **57**, as they do not appear to be interconvertible under the reaction conditions. It is proposed, then, that the spiroketal mixture **56** is the kinetically controlled product of hydrolysis of **43**.

The ^{3}J coupling of the methine proton to the carbon of the methyl group was a key argument in the assignment of the structure of the spiroketals **56a/b**. In order to confirm this assignment and for completion, ^{13}C n.m.r. experiments with full proton coupling were conducted on the bicyclic methylketals **58a** and **58b**. These compounds have a ^{4}J relationship between the methine proton and the carbon of the methyl group. The multiplet produced by the carbon of the methyl group of **58a** is shown in Figure 3 (cf. Figure 1).

Figure 3

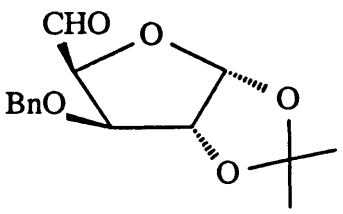


Bicyclic ketal **58b** gave a similar result with ^{1}J = 141Hz. The quartet is due to the three methoxy methyl protons directly bound to the carbon and the coupling constants compare with those obtained from the spiroketals (^{1}J = 140Hz). However, there is no evidence of any longer range coupling, providing further confirmation of the assignment of the spiroketals **56a** and **56b**.

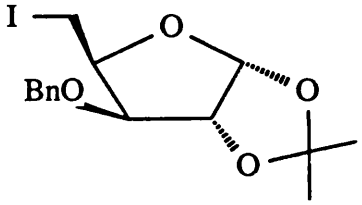
2.2d Reaction of metalated enol ether **41** with carbohydrate electrophiles

Having established methodology for: i) the introduction of carbon-carbon bonds to the anomeric centre of the simple dihydropyran **35** and ii) the selective release of the masked carbonyl functionality (as depicted in Scheme 7), the obvious extension of these studies was to investigate the compatibility of (i) and (ii) to reactions with carbohydrate electrophiles.

The two carbohydrates chosen were the furanose derivatives **63** and **64**, which both contain the stereochemistry at C(2), C(3) and C(4) that is present in the herbicidin natural products. The stereochemistry at C(1) is opposite to that present in the herbicidins but is that required for the introduction of an heterocyclic base unit.

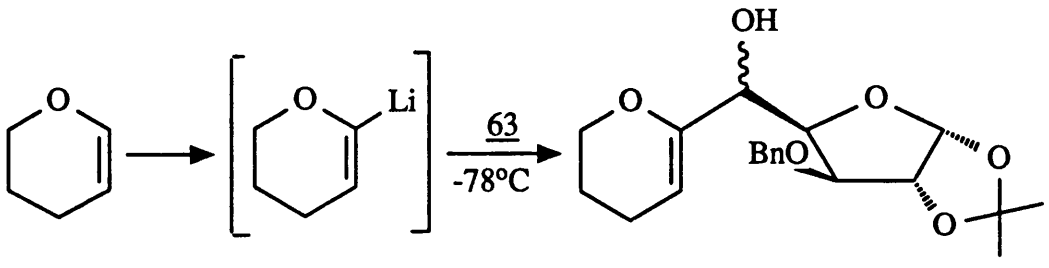


63



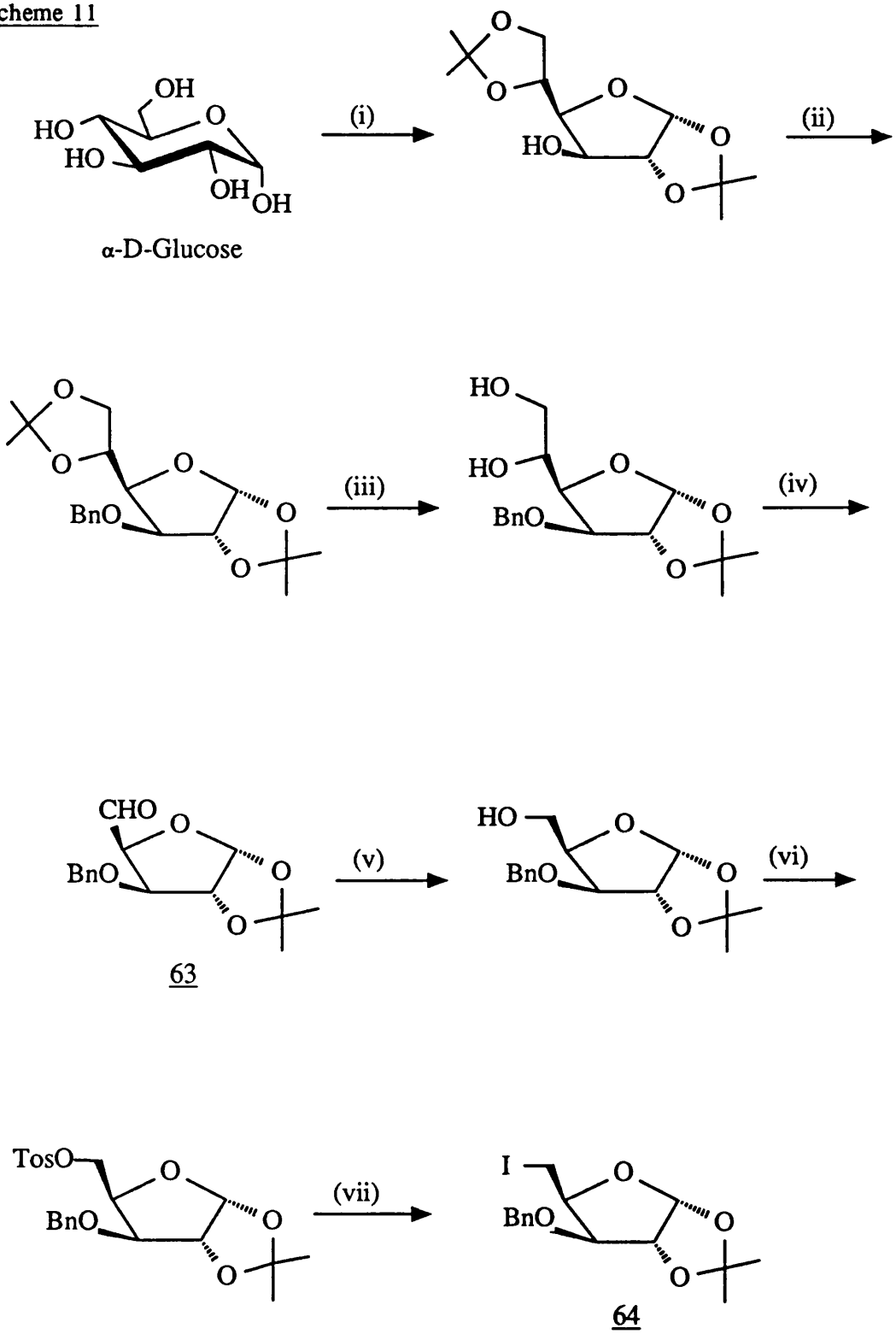
64

The synthesis of **63** utilising α-D-glucose[33] is shown in scheme 11 along with one of the approaches adopted to prepare the iodide **64**[35]. An alternative, more direct route to **64** is shown in Scheme 12, starting from 1,2-*O*-isopropylidene-D-xylofuranose. All of the reactions of Scheme 11 and 12 were taken from the literature and the spectral data obtained were in full agreement with those cited.



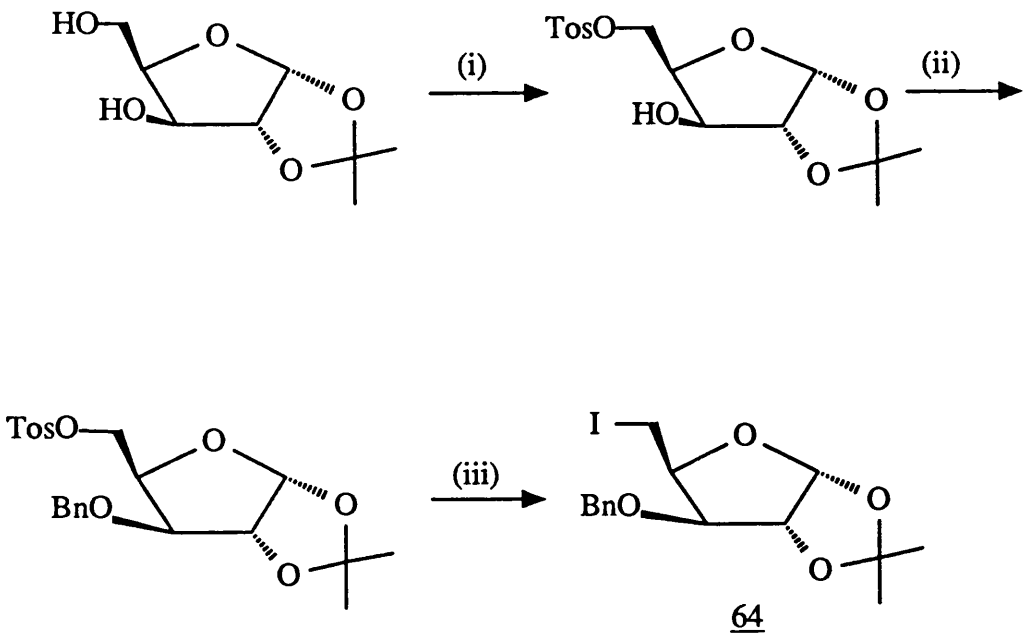
30 **65** **66**

Scheme 11



Reagents (i) H^+, acetone (56%)[33]; (ii) NaH, BnBr, Bu_4NI(cat)[35], (98%); (iii) AcOH, H_2O (99%)[33]; (iv) $NaIO_4$ (99%)[33]; (v) $NaBH_4$ (98%); (vi) TosCl, Pyridine (90%)[34]; (vii) NaI, acetone, 100°C sealed tube (64%).

Scheme 12



64

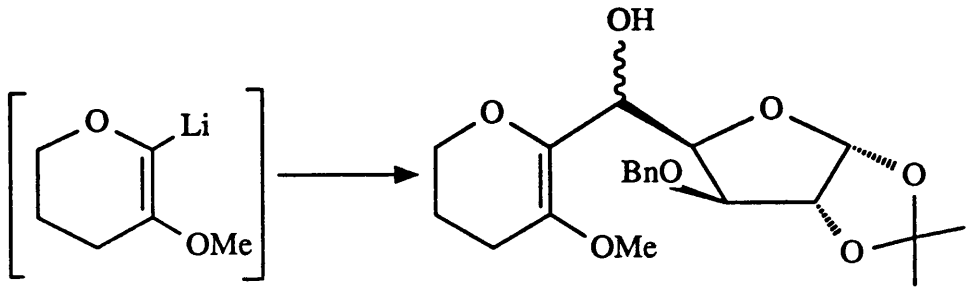
Reagents (i) TosCl, Pyridine (70%)[35]; (ii) NaH, BnBr, Bu_4NI(cat) (85%)[35]; (iii) NaI, acetone, 100°C sealed tube (64%).

As the starting enol ether **35** was not available in as large quantities as both **63** and **64**, it was decided to investigate the addition reactions using lithiated dihydropyran **65**. This readily available species was chosen as it was expected to have similar reactivity to our own lithiated dihydropyran **41**.

Lithiation was accomplished using the conditions outlined in Table 1, entry 7; i.e. **30** was treated with *n*-butyllithium at 0°C before the solution was warmed at 50°C to give the metalated dihydropyran **65**. The resulting anion was then cooled to -78°C before aldehyde **63** was added. This procedure yielded, after work up and

purification, adduct **66** as a 1:1 diastereomeric mixture in 50% combined yield. The two isomers were separable by chromatography but only one of them has been fully characterised due to the lability of the other.

Following on the success of this reaction, an attempt was made to extrapolate to the substituted dihydropyran **35**. Using the conditions describe above, **41** was generated and quenched at -78°C with aldehyde **43**.

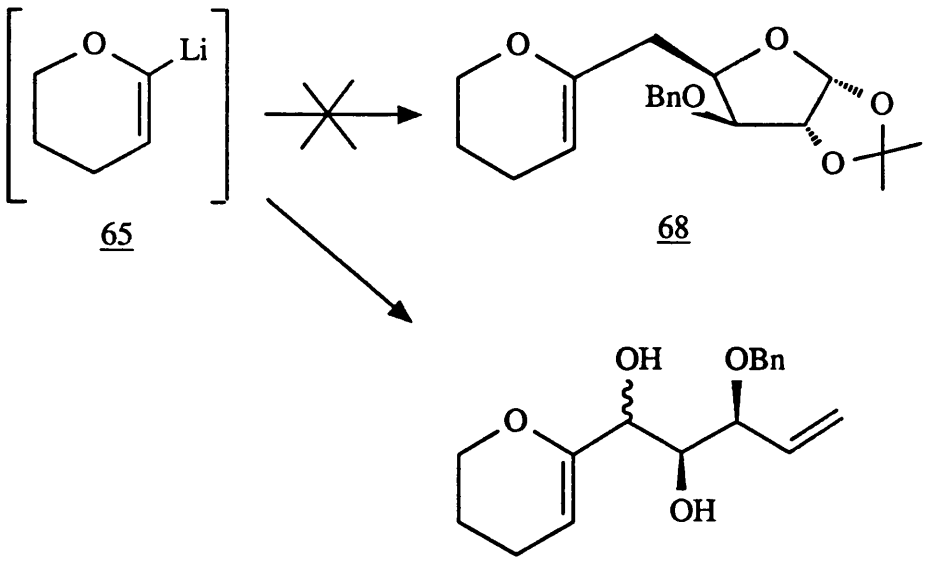


41 67

Although evidence was obtained for the presence of **67** as a reaction product (^{1}H n.m.r. spectrum on the crude product) attempts to purify it by preparative t.l.c. resulted in decomposition.

Attention was, therefore, turned to reaction of lithiated dihydropyran **65** with the iodofuranose derivative **64**. This electrophile promised to be more efficient for herbicidin synthesis, as a deoxygenation reaction would not be required after the coupling reaction.

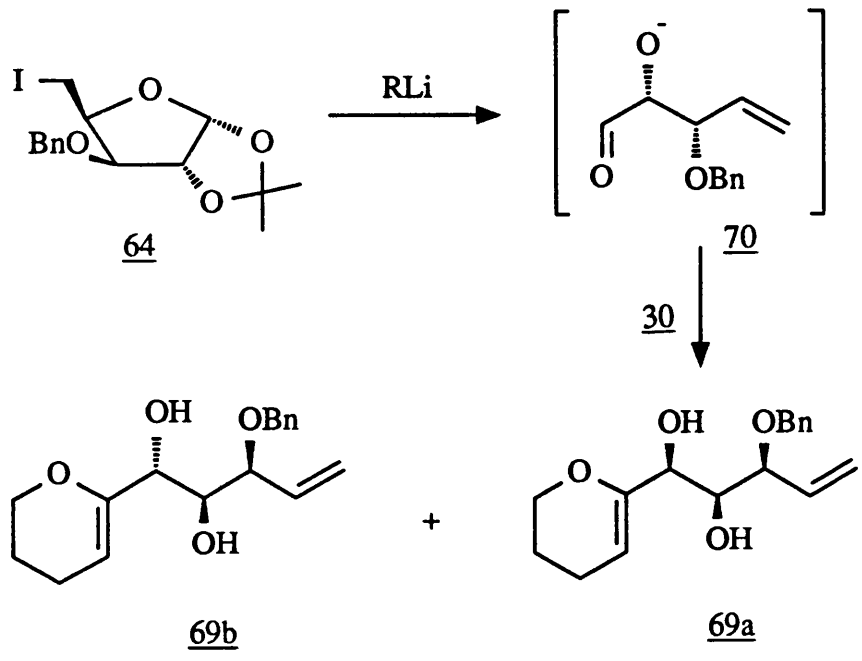
Generation of **65** in excess, as described above, was followed by addition of the iodide **64** at room temperature. From t.l.c. evidence it was apparent that reaction had occurred almost immediately to give two products of similar polarity. After work up and separation by chromatography, it was clear that neither of the two products was the expected adduct **68**. It was also apparent from the similarity in the spectroscopic data that the two compounds were diastereoisomers. Using a combination of 2D-COSY, proton-carbon correlation n.m.r. and mass spectroscopic evidence, it was possible to assign the structure of these products as a diastereomeric



mixture of adducts **69a/b**.

It is proposed that isomers **69a/b** arise as indicated in Scheme 13.

Scheme 13

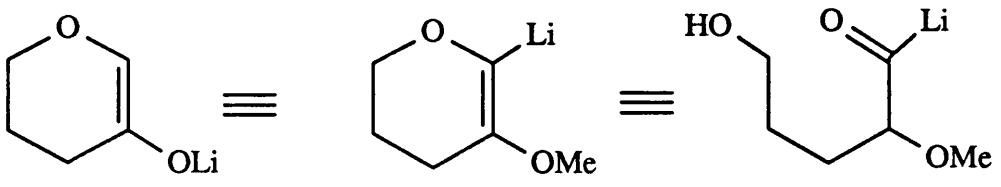


The ring opening reaction to give intermediate 70 could occur as a consequence of a halogen-metal exchange or reductive elimination. In the presence of excess lithiated dihydropyran 65, the 2:1 diastereomeric mixture of adducts **69a/b** were produced in a combined yield of 71%. Owing to this unsatisfactory result with simple dihydropyran, it was decided not to investigate reactions of the lithiated 5-methoxy-3,4-dihydro-2(*H*)-pyran **41** with iodofuranose **64**.

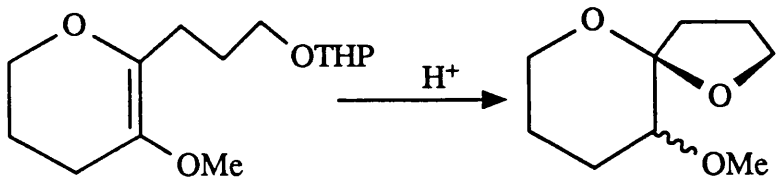
Although only preliminary results, our failure to successfully isolate the adduct 67, and the facile ring opening depicted in Scheme 13, tend to suggest that the metalated enol ether approach is not a practical synthetic strategy for the synthesis of the herbicidin natural products. This is borne out by the recent results of Schmidt[11] on the fully functionalised glucose derivative 22.

2.2e Summary

It has been shown that the metalated enol ether **41** can be used selectively as an equivalent of either the regiospecific enolate **10**, or the acyl anion **71**.

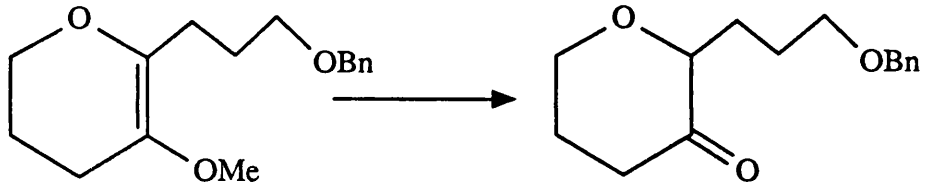


10 **41** **71**



43

Which of the two carbonyl equivalents metalated enol ether **41** actually represents can be controlled by manipulating protecting groups and the method of subsequent deprotection. Hydrolysis of adduct **43** reveals the acyl anion equivalence of **41**. However, treatment of adduct **45** with TMSI results in **41** acting as an enolate equivalent.



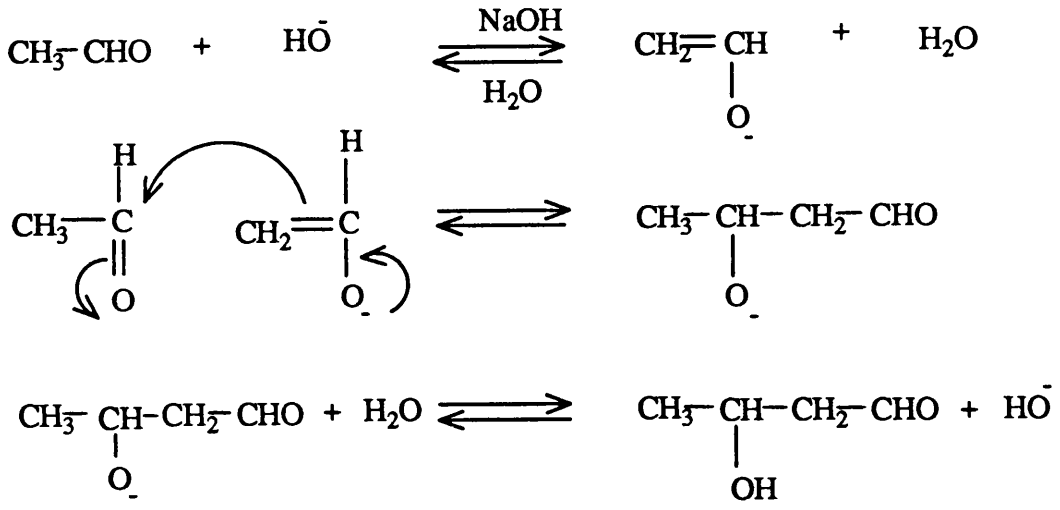
45

The ultimate aim of this programme is to develop chemistry applicable to the synthesis of the herbicidin natural products. The results of section 2.2d suggest that more detailed studies are required if this metalated enol ether approach is to be successfully used in a synthesis of the herbicidins. The use of different metalated species (e.g. higher order cuprates), or alternative leaving groups on the carbohydrate electrophile could be investigated but owing to limited time and the greater promise of the chemistry of Section 2.3, these alternatives have not been explored.

2.3 SILYL ENOL ETHER (ENOL SILANE) APPROACH

The addition of enolate ions to aldehydes and ketones, i.e. the aldol reaction, constitutes an important reaction in organic synthesis[36]. The mechanism of this reaction is outlined in Scheme 14, where the self-condensation of ethanal has been considered.

Scheme 14

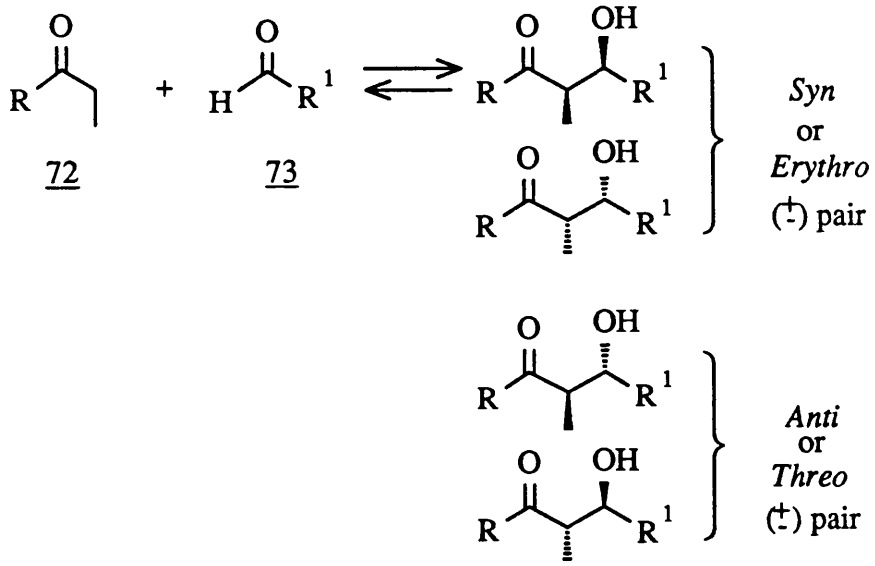


Unfortunately, the cross condensation of more elaborate carbonyl compounds can be problematical for a number of reasons;-

i) Self condensation of both carbonyl components is possible and four products are potentially available.

ii) Unsymmetrical carbonyl compounds can give rise to two regioisomeric enolates which can result in additional possible products.

iii) Enolisation of a prochiral carbonyl compound 72 followed by condensation with an aldehyde or ketone such as 73, can result in four stereoisomeric products.



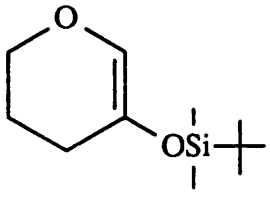
72 73

Control of both diastereoselectivity and enatioselectivity is therefore a problem in this type of reaction.

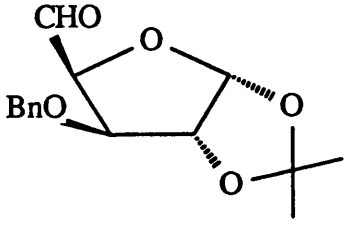
The use of pre-formed enol derivatives provides a way of overcoming these problems[37]. Among the pre-formed enol derivatives used, have been enolates of magnesium, lithium[38], zirconium[39] and tin[40], silyl enol ethers[41] and enol borinates[42].

Of interest to our studies is the use of silyl enol ethers[43], and in particular, the Lewis acid mediated reactions of these species[2].

As described in section 2.2 the silyl enol ether that was of particular interest to us was 9, and for this approach to be a successful one, 9 must be capable of condensing with either aldehyde 63 or a suitable derivative thereof.



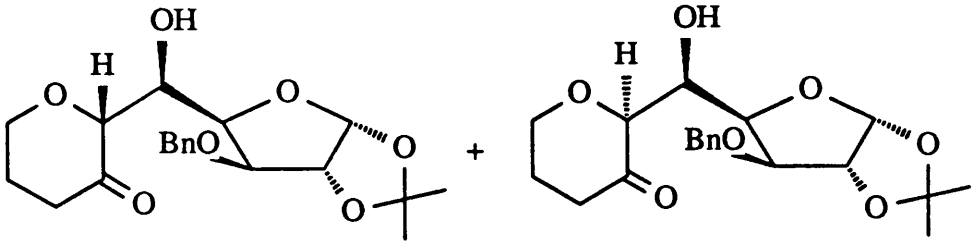
9



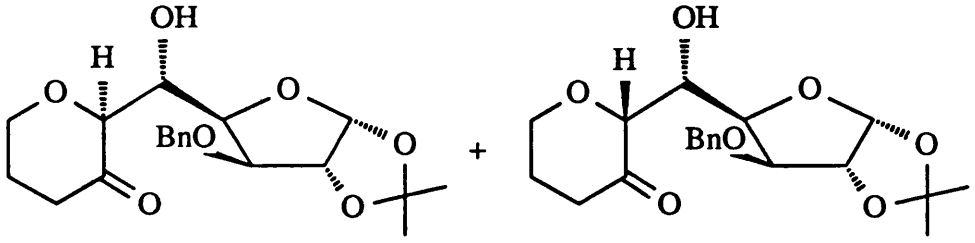
63

In the presence of a Lewis acid four stereoisomeric products are available from reaction of silyl enol ether 9 with aldehyde **63** as illustrated in Scheme 15. Two of

Scheme 15

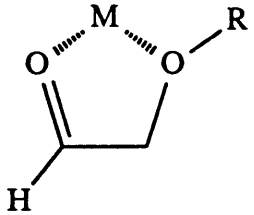


Non-chelation or β-chelation control



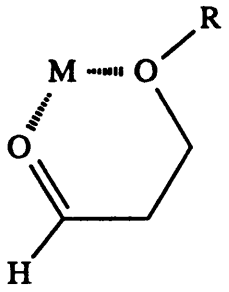
α-Chelation control

these products can arise from non-chelation control[44] and the second pair from α-chelation (74)[44]. Furanose aldehyde **63** is also capable of *β*-chelation (75) and reaction of enol ether 9 with this chelate is expected to give the same diastereomeric mixture that would be given by non-chelation control.



α-chelation

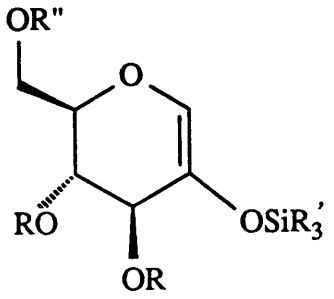
74



β-chelation

75

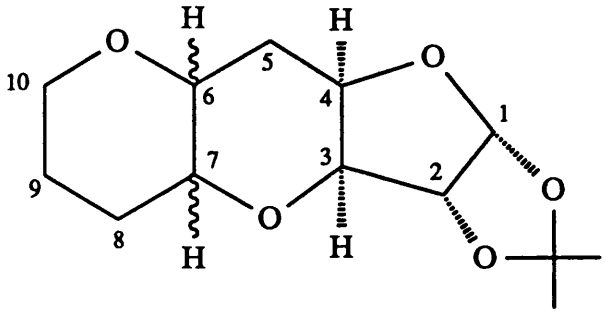
A study of the stereochemical outcome of this Lewis acid-mediated reaction with various Lewis acids would, therefore, be interesting[45], but it should be remembered that this represents only a model system. Any stereoselectivity observed in the reaction of enol ether **9** with aldehyde **63** may not be applicable when fully substituted carbohydrate derived pyranose enol ether derivatives such as **6** are reacted with **63**. It should also be noted that the stereochemistry of the secondary



6

alcohol created in this reaction is, in terms of a synthesis of the herbicidins, unimportant as it would have to be removed.

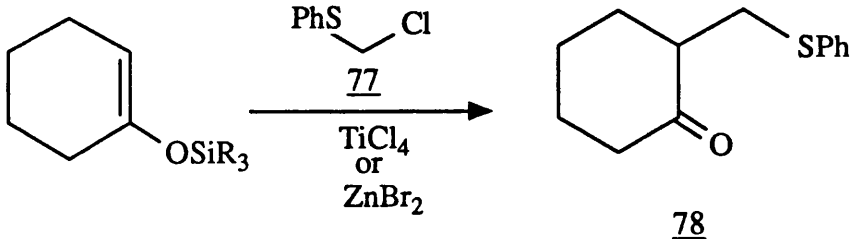
When these studies were conducted, therefore, the stereochemistry was only of secondary importance. Our primary aim being to introduce regiospecifically a carbon-carbon bond to the anomeric centre of pyran-3-one **12**. Having introduced the carbon-carbon bond a simple deprotection and a deoxygenation of the secondary hydroxyl group at C(5) would provide access to the unsubstituted analogue of the



76

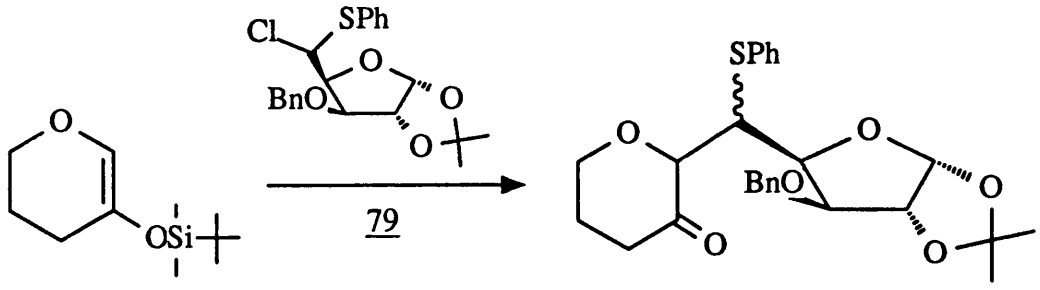
carbohydrate portion of the herbicidins **76**. A synthesis of this compound was, therefore, the aim of this study.

Silyl enol ethers have also been seen to undergo Lewis acid mediated reactions with α-chloroalkylphenylsulphides[46], e.g. **77**. The product of such a reaction is a phenylsulphide, e.g. **78**, the phenylthio moiety of which can be conveniently remov-



78

ed with Raney nickel. Therefore, if silyl enol ether **9** could be coupled with α-chlorophenylsulphide **79**, we would have a species **80** which could conceivably be transformed into the unsubstituted analogue of the carbohydrate portion of the herbicidins **76**. This entry into **76** promises to be more convenient than the aldol approach as it avoids the deoxygenation of the secondary alcohol function at C(5) which can often be problematical (see below).

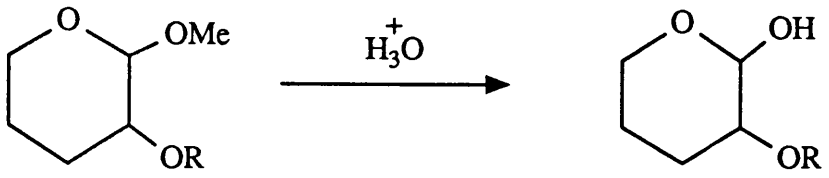


9 80

The objectives of this second study were therefore :-

a) Synthesis of 5-(*O*-*tert*-butyldimethylsilyl)-3,4-dihydro-2(*H*)-pyran **9**.

In Section 2.2a a general synthesis of 5-alkoxy-3,4-dihydro-2(*H*)-pyrans was described. Included in this synthesis is an acid hydrolysis to convert the methyl acetal to the corresponding hemiacetal.



This reaction could not, however, be used in a synthesis of a 5-*O*-silyl derivative, as oxygen-silicon bonds were anticipated to be labile under these conditions[47].

Using a similar approach to that described in section 2.2a, but with an alternative entry into the desired hemiacetal, an efficient synthesis of the title enol ether **9** has been developed.

b) Aldol addition reactions of silyl enol ether **9**.

The addition of silyl enol ether **9** to benzaldehyde and the furanose aldehyde **63** has been investigated. The effect of both tin tetrachloride ($SnCl_4$) and titanium tetrachloride ($TiCl_4$) on the stereoselectivity of the reaction with **63** has also been studied.

Furthermore, attempts to carry adducts of aldehyde **63** through to the simplified analogue of the carbohydrate portion of the heribicidins **76** will be described.

c) Synthesis of α-chloroalkylphenylsulphides[48].

As described above, addition reactions of silyl enol ether 9 to 5-chloro-5-phenylthio furanose derivatives, such as **79**, promised to be an efficient route to the simple herbicidin analogue 76. However, both the α-chloroalkylphenylsulphides and the phenylsulphides from which they are derived were previously unknown.

The synthesis of two α-chloroalkylphenylsulphides has been achieved.

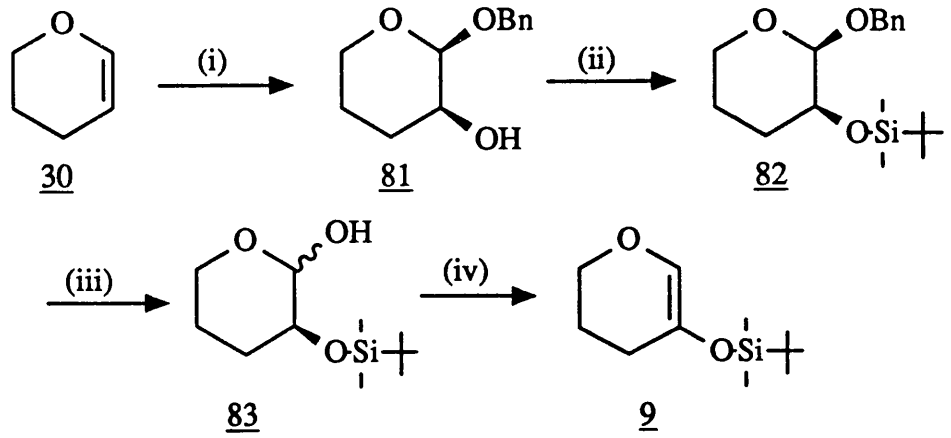
d) Addition reactions of silyl enol ether **9** to α-chloroalkylphenylsulphides.

The addition of silyl enol ether **9** to chloromethylphenylsulphide 77 and two 5-chloro-5-phenylthio furanose derivatives has been investigated. Experiments involving both titanium tetrachloride ($TiCl_4$) and zinc bromide ($ZnBr_2$) will be described.

An indication of the stereochemical outcome of these reactions along with attempts to transform adducts into the simplified analogue of the carbohydrate portion of the herbicidins **76** are reported.

2.3a Synthesis of 5-(*O*-*tert*-butyldimethylsilyl)-3,4-dihydro-2(*H*)-pyran 9

Scheme 16



Reagents (i) *m*CPBA, BnOH, (58%); (ii) *t*BDMSCl, DBU, CH_2Cl_2, (94%); (iii) H_2, 10% Pd/C, (86%); (iv) MsCl, Et_3N, reflux, (80%).

Silyl enol ether **9** was synthesized using a strategy similar to that described in section 2.2a for the synthesis of the 5-(*O*-methyl) **35** and 5-(*O*-benzyl) **34** analogues. The critical modification was the replacement of methanol for benzyl alcohol (BnOH) in the initial oxidation reaction of dihydropyran **30**; this allowed deprotection of the anomeric hydroxyl group under non-hydrolytic conditions.

Using a modification of Brown's procedure[16], dihydropyran **30** was treated with *m*-chloroperoxybenzoic acid (*m*CPBA) in benzyl alcohol (BnOH) at -5°C to give the novel 2-(*O*-benzyl)-3-hydroxy acetal **81** in 58% yield. The free secondary hydroxyl residue was then silylated in 94% yield by treatment of tetrahydropyran **81** with *tert*-butyldimethylsilyl chloride (*t*BDMSCl) and 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) in dichloromethane[49].

The anomeric hydroxyl group was then efficiently deprotected by subjecting the disubstituted tetrahydropyran **82** to hydrogenolysis, to give hemiacetal **83** in 86% yield.

Dehydration of **83** was achieved by treating it with methanesulphonyl chloride (MsCl) and triethylamine (Et_3N) in chloroform at 0°C. Heating at reflux then furnished the key silyl enol ether **9** in 80% yield.

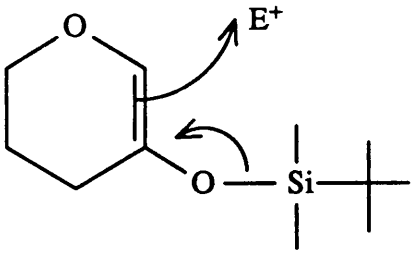
The stereochemistry of **81**, **82** and **83** has not been discussed, as it is of no consequence to the outcome of this synthetic scheme.

2.3b Aldol addition reactions of silyl enol ether 9

A logical progression from the metalated enol ether approach to the formation of carbon-carbon bonds at the anomeric centre of pyran-3-one **12**, involves cleavage of the enol ether and formation of the new carbon-carbon bond during the same synthetic step. This transformation can be achieved using silyl enol ethers under Lewis acid mediation[2].

As a preliminary experiment we chose to investigate the reaction of the silyl

Figure 4

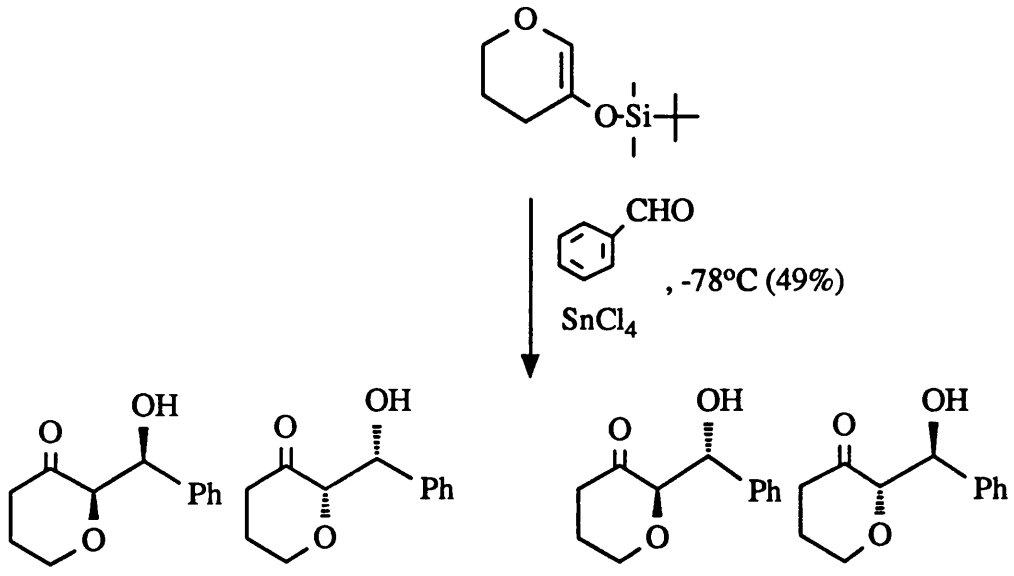


E^+ = carbon electrophile

enol ether **9** with benzaldehyde.

Using the conditions described by Heathcock[2d] ($SnCl_4$, -78°C, CH_2Cl_2), reaction of silyl enol ether **9** with benzaldehyde gave a chromatographically inseparable mixture of ketols **84a-d**, Scheme 17, as the major product in 49% yield.

Scheme 17



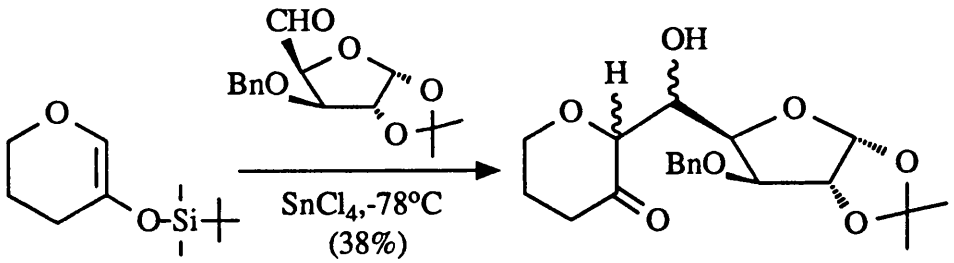
Syn/Erythro *Anti/Threo*

84a **84b** **84c** **84d**

From ^1H n.m.r. evidence we concluded that this product was a 3:2 mixture of *syn:anti* diastereomers. This assignment was based on the chemical shifts and coupling constants[50] of the benzylic protons (*syn* δ 5.22, d, J = 3.5Hz; *anti* δ 4.95, d, J = 7.5Hz).

Following the success of this preliminary experiment, we chose to investigate the addition of silyl enol ether **9** to the furanose aldehyde **63**. Completion of this coupling, as described earlier, would provide a possible entry into the simple analogue of the carbohydrate portion of the herbicidins **76**.

Using a similar procedure to that used for the reaction of silyl enol ether **9** with benzaldehyde, furanose aldehyde **63** was treated with tin tetrachloride in dichloromethane at -78°C. Addition of silyl enol ether **9** gave a complex mixture of products, from which one major component **85** was isolated.



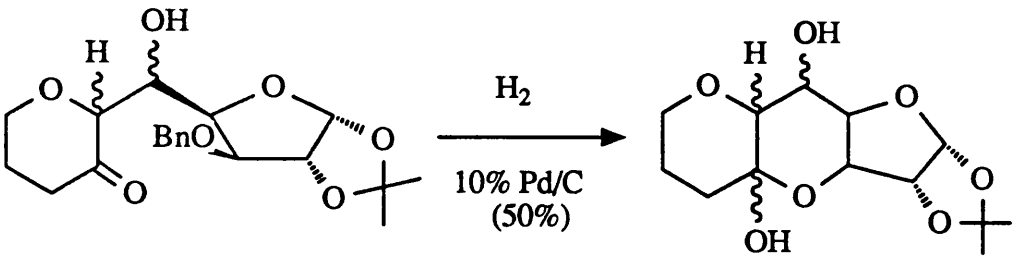
85a/b

From ^1H n.m.r. data it was apparent that the chromatographically homogeneous component isolated was a 1:1 mixture of only two of the four diastereomers possible from the reaction (Scheme 15). Overlap of complex resonances in the ^1H n.m.r. spectrum along with our failure to separate the two diastereomers **85a/b** precluded assignment of the stereochemistry of these products.

Debenzylation (H_2, 10% Pd/C) of the mixture of adducts **85a/b** resulted in the

isolation of two furo-pyrano-pyrans **86a/b** (50% combined yield) that were now readily separable by flash chromatography.

Scheme 18



85a/b

(Inseparable by chromatography)

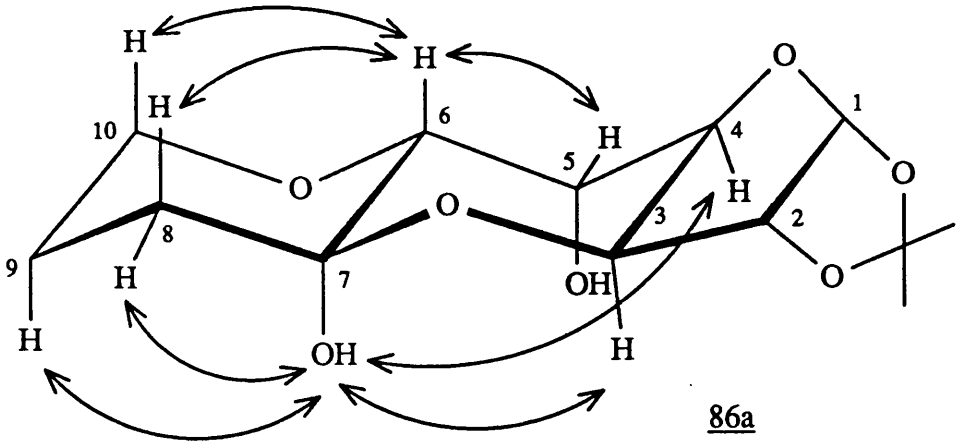
86a/b

(Separable by chromatography)

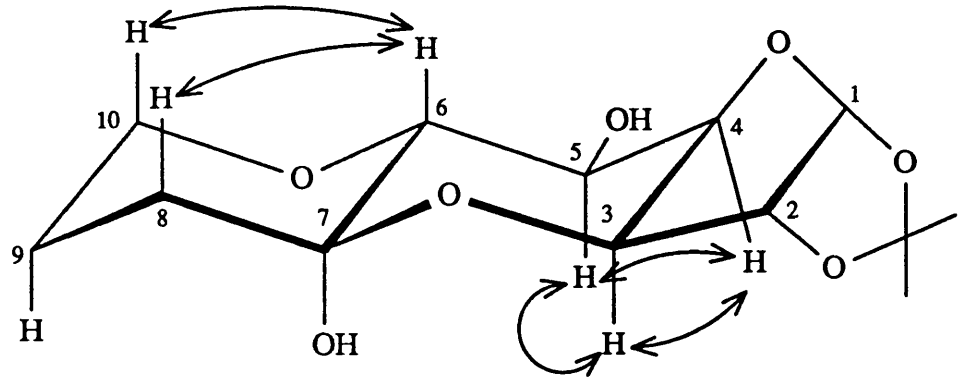
This was an interesting result, as ring closure to the hemiketal **86**, generates a new chiral centre and four products are therefore possible from the reaction shown in Scheme 18; i.e. both diastereomers of **85** can generate two diastereomers of **86**. Our result is presumably a consequence of the conformational constraints applied by the fixed stereochemistry of the furanose ring and also by the hydroxyl group of the hemiketal, adopting an axial relationship with respect to the adjacent ring oxygen; i.e. the thermodynamic influence of the anomeric effect[51].

Although both furo-pyrano-pyrans **86a** and **86b** were crystalline, all attempts to obtain crystals suitable for X-ray crystallographic analysis were unsuccessful. Definitive determination of the stereochemistry of these tricycles has therefore been precluded. We have however, been able, tentatively, to assign their structure based on nuclear Overhauser effect (n.O.e.) experiments. Both structures along with the key enhancements are illustrated in Figure 5. Other enhancements observed have been included in Table 3.

Figure 5



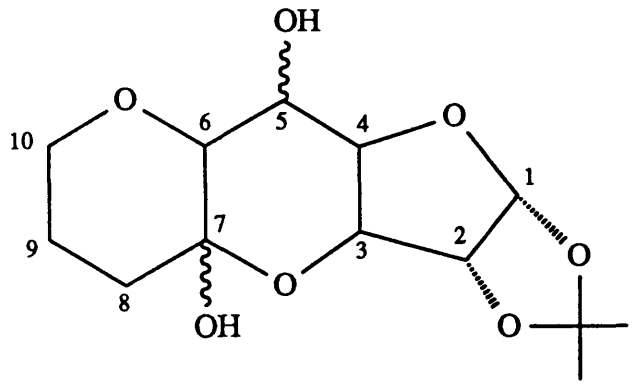
86a



86b

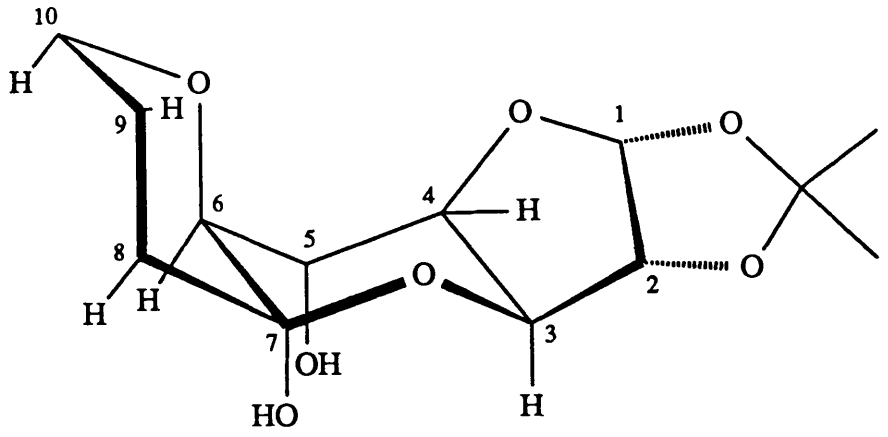
The evidence for structure **86a** is strong. The large negative n.O.e. between the two hydroxyl protons suggests that these groups may be hydrogen bonded, lending support to the theory that both groups are axial with respect to the central six membered ring. Furthermore, an n.O.e. between C(5)OH and C(3)H would be highly unlikely unless the hydroxyl group was in an axial conformation. Additional evidence for the structure of **86a** comes from the n.O.e.s observed from C(6)H and C(7)OH into both six membered rings.

Table 3



86a		86b	
^{1}H Irradiated	^{1}H Enhanced (%)	^{1}H Irradiated	^{1}H Enhanced (%)
C(3)H(δ 4.56)	C(2)H(3.0%) C(4)H (5.5%) C(7)OH (1.0%)	C(4)H(δ 4.40)	C(3)H (6.5%) C(5)H (10%)
		C(5)H (δ 4.03)	C(3)H (2.5%) C(4)H (6.5%)
C(4)H (δ 4.34)	C(3)H (6.5%) C(5)H (2.0%)		
		C(6)H (δ 3.25)	C(8)Hax (13%) C(10)Hax (3%)
C(5)H (δ 4.29)	C(6)H (6.0%)		
C(5)OH (δ 4.16)	C(7)OH (~87%) C(3)H (6.5%) C(4)H (2.0%)		
C(6)H (δ 3.34)	C(5)H (6.0%) C(8)Hax (6.0%) C(10)Hax (6.0%)		
C(7)OH (δ 5.53)	C(3)H (7.0%) C(4)H (3.0%) C(5)OH (~90%) C(8)Heq (5.0%) C(9)Hax (4.0%)		
C(10)Hax (δ 3.52)	C(6)H (7.0%) C(10)Heq (20%)		

An alternative structure proposed for **86a**, which fits most of the n.O.e. data, is **87**.



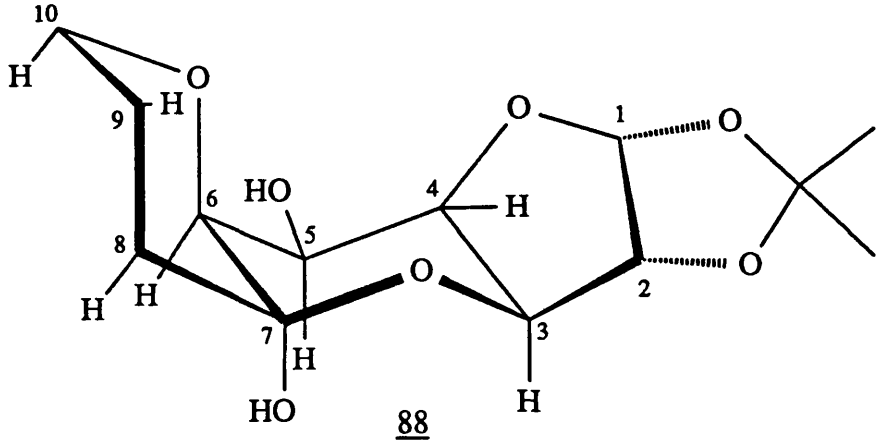
87

In this structure, however, an n.O.e. from C(7)OH to C(9)Hax would appear very unlikely. One might also expect an n.O.e. from C(7)OH to C(6)H, an enhancement which was not present in our results.

It was based on these results that one of the products of hydrogenolysis of **85a/b** was assigned the structure **86a**.

The evidence for the assignment of **86b** is somewhat more tentative. This was due to the fact that neither hydroxyl proton produced a distinct resonance in the ^1H n.m.r. spectrum. This restricted the range of n.O.e. experiments performed.

An alternative structure which complies with all the n.O.e. data is **88**.



88

The n.O.e. from C(5)H to C(3)H suggests that C(5)H is in the axial orientation and that C(5)OH is equatorial. The n.O.e.s from C(6)H to both C(8)Hax and C(10)Hax suggests that C(6)H is axial with respect to the terminal six membered ring. Both of these key pieces of evidence apply equally to structures **86b** (Figure 5) and **88**. The lack of protons which have n.O.e.s into both six membered rings hinders distinction between the two proposed structures.

Table 4

Proton	Tricycle **86a** δ; multiplicity; J	Tricycle **86b** δ; multiplicity; J
C(6)H	3.34; d; 3Hz	3.25; d; 10Hz
C(5)H	4.30; brs	4.03; dd; 10,4 Hz
C(4)H	4.34; t; 2.5 Hz	4.39; dd; 4,2 Hz
C(3)H	4.46; d; 1.5 Hz	4.29; d; 2 Hz

If we consider the spectral data of Table 4, and in particular the coupling constant produced by coupling of C(5)H and C(6)H, we are able to make some distinction between **86b** (Figure 5) and **88**.

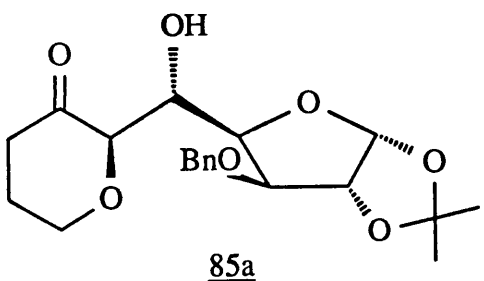
In **86b**, C(5)H and C(6)H have a *trans* diaxial relationship to one another. One would thus predict a large coupling constant (J), of approximately 9-13Hz[52], between these two protons. The observed coupling constant of 10Hz is therefore supportive of structure **86b**.

In structure **88**, C(5)H and C(6)H have a gauche relationship to one another. One might then predict a relatively small coupling constant, of approximately 2-8Hz[52], between these two protons (cf. **86a**). This structure does not, therefore, fit the observed data.

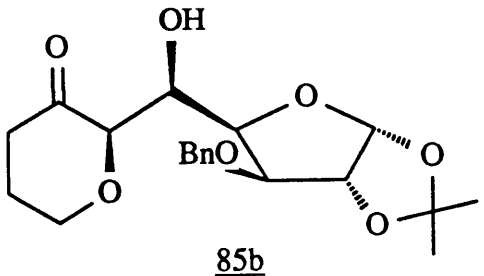
This evidence alone is insufficient to assign with confidence the structure of **86b** as shown in Figure 5. Further evidence will be provided, however, which excludes **88** as a possible product of hydrogenolysis of **85a/b**.

If the proposed structures of tricycles **86a** and **86b** are correct, then it would appear that the two major products of the tin tetrachloride mediated reaction of aldehyde 63 with silyl enol ether 9 are adducts **85a** and **85b** (Scheme 19).

Scheme 19



85a
(gives tricycle 86a)
Anti
α-chelation



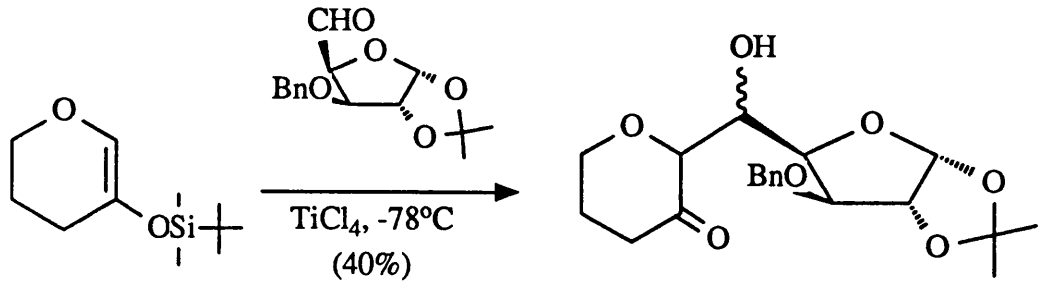
85b
(gives tricycle 86b)
Syn
β-chelation

In the wake of these interesting results, we decided to investigate the effect of titanium tetrachloride on the stereoselectivity of this aldol reaction.

Treatment of a solution of furanose aldehyde **63** with titanium tetrachloride at -78°C followed by addition of silyl enol ether **9** gave a complex mixture of reaction products. However, two chromatographically separable components predominated in approximately equal amounts (cf. reaction with tin tetrachloride; only major component a mixture of two diastereomers). Spectroscopic analysis revealed that these two components were single stereoisomers of the aldol adduct **85** and they will be labeled **85c** and **85d** to distinguish them from the products of the reaction with tin tetrachloride.

By comparison of the ^1H n.m.r. spectrum of the **85a/b** mixture of adducts, with those of **85c** and **85d**, it was apparent that one of the new products **85c** was common to reaction with both tin tetrachloride and titanium tetrachloride. It was important to determine which of adducts **85a/b** was the common product. This was

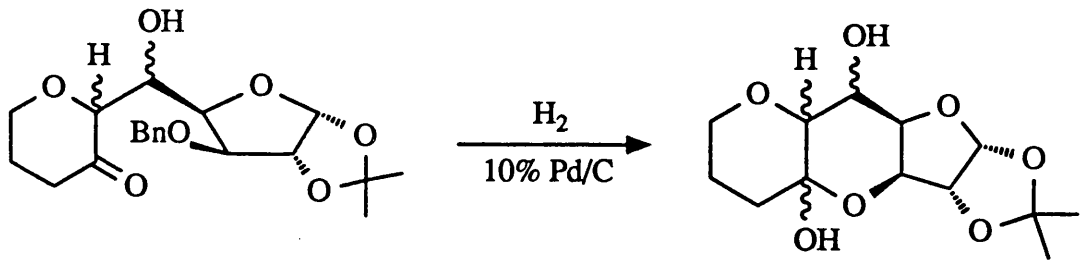
Scheme 20



9 85a , 85d

most conveniently achieved by removal of the benzyl group of **85c**. For completion **85d** was also debenzylated.

Scheme 21



85c ⟶ 86c (65%)

85d ⟶ 86d (56%)

Adduct **85c** was reductively debenzylated (H_2, 10%Pd/C) to give furo-pyrano-pyran **86c** in 65% yield after purification. Full spectroscopic analysis revealed that

this tricycle was identical to **86a**.

Adduct **85d** gave a novel furo-pyrano-pyran **86d** in 56% yield after purification. As with tricycles **86a** and **86b**, tricycle **86d** was crystalline, but attempts to obtain crystals suitable for X-ray crystallographic analysis were unsuccessful. N.O.e. experiments on **86d** were also inconclusive. The only evidence for the structure of **86d** was a comparison of its coupling constants with those of tricycles **86a** and **86b**. All the relevant data have been included in Table 5.

Table 5

Proton	Tricycle **86a** (400 MHz) δ; multiplicity; J	Tricycle **86b** (400 MHz) δ; multiplicity; J	Tricycle **86d** (270 MHz) δ; multiplicity; J
C(6)H	3.34; d; 3Hz	3.25; d; 10Hz	3.15; dd; 2.5,1 Hz
C(5)H	4.30; brs,	4.03; dd; 10,4 Hz	3.88; t; 2Hz
C(4)H	4.34; t; 2.5 Hz	4.39; dd; 4,2 Hz	3.98; t; 2 Hz
C(3)H	4.46; d; 1.5 Hz	4.29; d; 2 Hz	4.29; d; 2.5 Hz

Two structures with which the data for **86d** are consistent are **87** and **88**. These can be distinguished from other proposed structures by the 1Hz coupling to C(6)H. We propose that this is a W coupling [52] from C(4)H (supported by cross-peak in COSY ^{1}H n.m.r. spectrum). Although the expected C(6)H to C(4)H coupling cannot be seen in this case, the C(5) deoxygenated equivalent (synthesis presented later) has an obvious W coupling from C(6)H to C(4)H.

Unfortunately, this assignment is very speculative and no proposal can be made about the stereochemistry of the secondary hydroxyl group without further investigation.

In summary, it has been shown that the tin tetrachloride and titanium tetrachloride mediated reactions of furanose aldehyde **63** with silyl enol ether **9** show some degree of stereoselectivity.

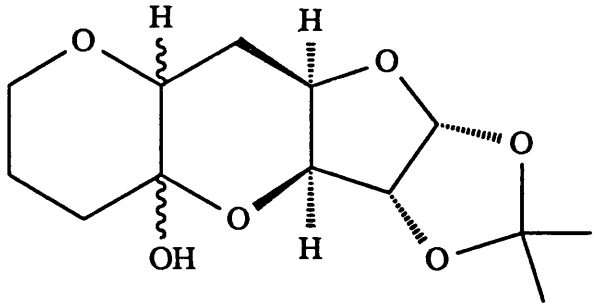
Reaction with tin tetrachloride provides only two of four possible adducts, and

their stereochemistry has been tentatively assigned as **85a** and **85b** (Scheme 19).

Reaction with titanium tetrachloride also provides only two adducts. One adduct is common to both tin tetrachloride and titanium tetrachloride reactions, i.e. **85c** = **85a**, and the second is unique to reaction mediated by titanium tetrachloride. As yet the stereochemistry of this second product is unknown.

Until more positive evidence (e.g. X-ray data) is available for the stereochemistry of the aldol adducts **85a/b** and in particular **85d**, a rationale for the stereoselectivity observed is precluded.

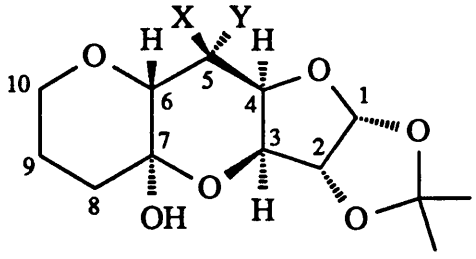
One of the aims of this study was to synthesize a simple analogue of the carbohydrate portion of the herbicidins. This was depicted earlier with the stereochemistry undefined, as **76**.



76

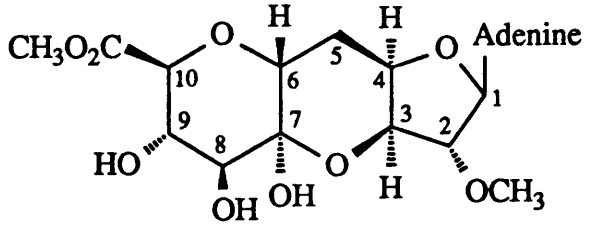
In Scheme 22 it can be seen that the proposed structures for **86a** and **86b** have the stereochemistry at C(6) and C(7) that is present in the herbicidins.

Scheme 22



86a X=H, Y=OH

86b X=OH, Y=H

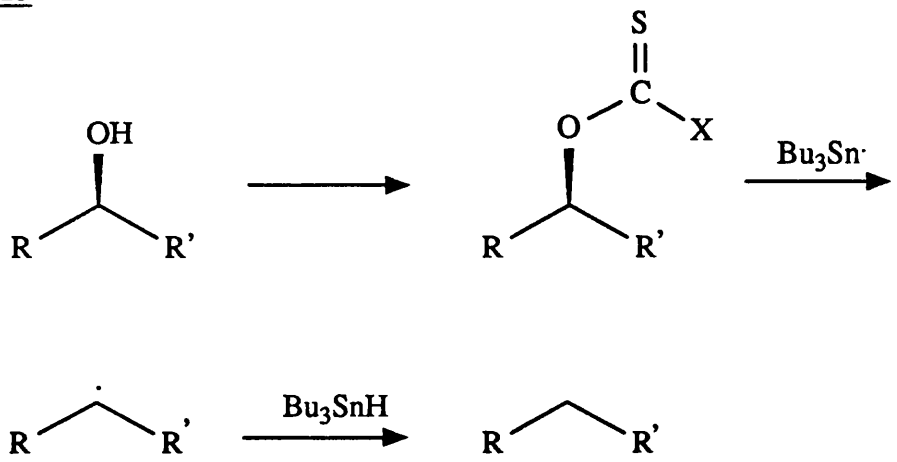


Herbicidin B

Deoxygenation of the C(5) secondary hydroxyl group of **86a** or **86b** would therefore provide access to the isomer of **76**, which has the desired stereochemical relationships.

Deoxygenation of secondary alcohols is now commonly performed via radical processes[53] such as that outlined in Scheme 23.

Scheme 23



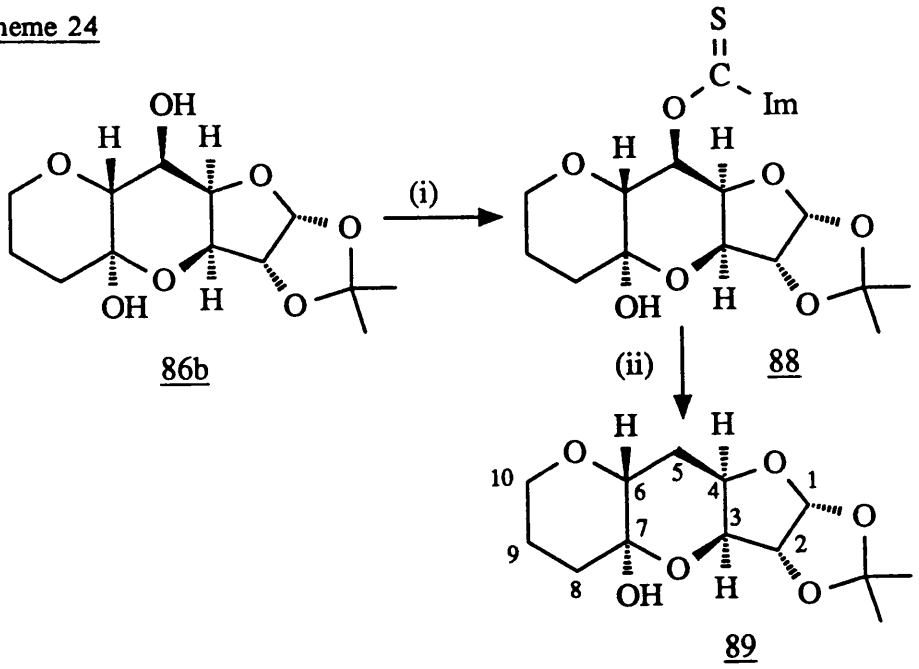
Although many variations of this procedure are available, we chose to investigate the radical cleavage of the thiocarbonyl imidazole derivative[53,54]; i.e. Scheme 23, **87**, X = imidazole (Im). This particular process was chosen because of the mild, neutral conditions that may be employed[54].

As equatorial hydroxyl groups are generally more reactive than their axial counterparts, we decided to begin our investigations on tricycle **86b**.

Treatment of tricycle **86b** with thiocarbonyl diimidazole [$(Im)_2CS$] in *N,N*-dimethylformamide resulted in clean conversion to the thiocarbonyl imidazole derivative **88** in 55% yield. This intermediate was then heated at reflux with tributyltin hydride (Bu_3SnH) and a catalytic amount of azobisisobutyronitrile (AIBN). Although this was not a clean reaction, one product predominated which was subsequently shown to be a tricycle of the type **89**.

As yet no physical evidence has been obtained to prove the stereochemistry of

Scheme 24



Reagents (i) $(Im)_2CS$, DMF (55%); (ii) Bu_3SnH, AIBN (cat), toluene, reflux (30%).

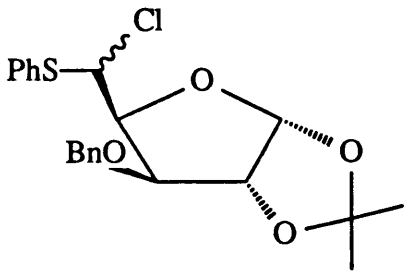
tricycles **88** and **89**. In Scheme 24 it has been assumed that the stereochemistry at C(6) and C(7), in these two compounds, remains unaltered by reactions (i) and (ii). This assumption can be justified, however, as neither process is expected to cause epimerisation of C(6), and C(7) has the thermodynamically favourable axial orientation of the hydroxyl function to the central six membered ring.

All attempts to form the thiocarbonyl derivative of **86a** have so far failed. This lack of reactivity would lend support to the proposal that the C(5) hydroxyl group adopts an axial configuration. Conversely, the relatively high reactivity of the C(5) hydroxyl of **86b** supports the assignment of its equatorial configuration.

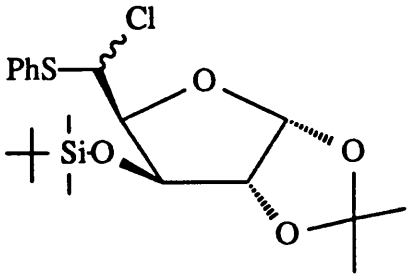
In summary, it would appear that the Lewis acid mediated aldol approach to the synthesis of simple analogues of the carbohydrate portion of the herbicidins is a successful one, if not an efficient one. Extrapolation of these studies to the use of fully substituted carbohydrate-derived silyl enol ethers is currently under investigation.

2.3c Synthesis of 5-chloro-5-phenylthio furanose derivatives

As described at the beginning of section 2.3, we were also interested in the Lewis acid mediated reactions of α-chloroalkylphenylsulphides[46,48], such as 79 with silyl enol ether 9. An approach to the synthesis of 5-chloro-5-phenylthio furanose derivatives was therefore required.



79

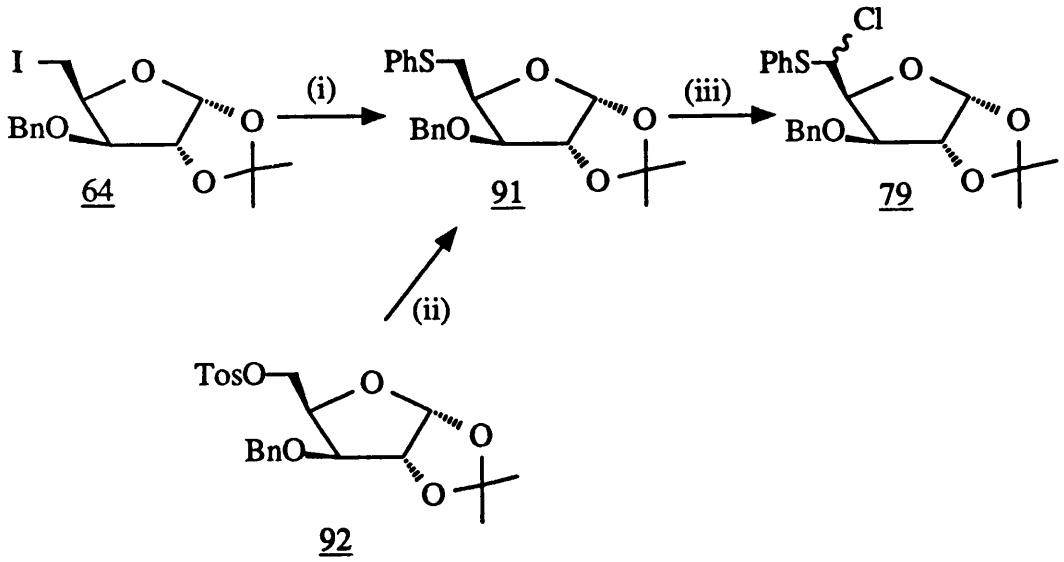


90

Two α-chloroalkylphenylsulphides were chosen, the 3-(*O*-benzyl) derivative 79 and the 3-(*O*-*tert*-butyldimethylsilyl) derivative 90, which both possess the stereochemistry required for the herbicidins.

The synthesis of the 5-chloro-5-phenylthio furanose derivative 79 is outlined in Scheme 25. Starting materials 64 and 92 were prepared as described in section 2.2d.

Scheme 25



64 91 79 92

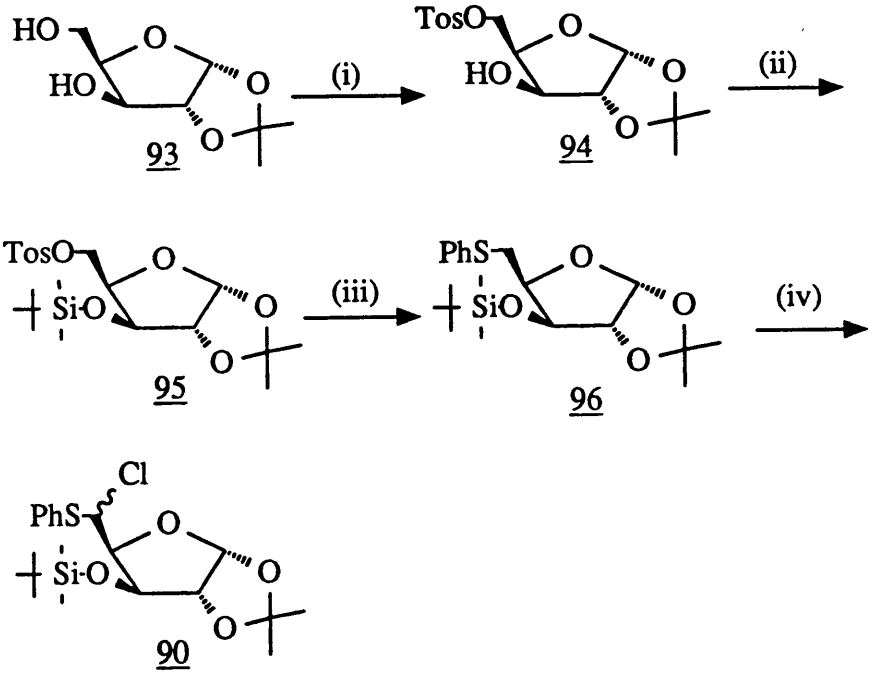
Reagents (i) PhSH, DBU, (r.t., 2h) (85%); (ii) PhSH, DBU, (r.t., 12h)) (86%); (iii) NCS, CCl_4, 4h.

Treatment of either the 5-iodo derivative **64** or the corresponding tosylate 92 with thiophenol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[55], gave phenylsulphide **91** in 85% and 86% yields respectively. Although the same conditions were used the tosylate (12h) reacted somewhat slower than the iodide (2h).

Conversion of phenylsulphide **91** to α-chlorosulphide **79** was achieved by treating a solution of **91** in carbon tetrachloride with *N*-chlorosuccinamide (NCS)[48]. This procedure gave a diastereomeric mixture of α-chlorosulphides **79**, in what appeared to be a quantitative reaction by t.l.c.. After isolation the crude mixture 79 was reacted directly with silyl enol ether **9** under Lewis acid mediation. The results of such reactions are reported in section 2.3d.

Our approach to the synthesis of the 3-(*O*-*tert*-butyldimethylsilyl)-5-chloro-5-phenylthio furanose derivative **90** is outlined in Scheme 26.

Scheme 26



Reagents (i) TosCl, Py (70%); (ii) *t*BDMSCl, DBU (98%); (iii) PhSH, DBU, (50°C, 16h) (61%); (iv) NCS, CCl_4.

The primary hydroxyl group of 1,2-*O*-isopropylidene-D-xylofuranose 93 was selectively protected/activated via treatment with *p*-toluenesulphonyl chloride (TosCl) and pyridine (Py) to give the tosylate **94** in 70% yield[34]. Protection of the secondary hydroxyl group was subsequently achieved by treatment of tosylate **94** with *tert*-butyldimethylsilyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene in dichloromethane[49]. This procedure furnished the 3-(*O*-*tert*-butyldimethylsilyl) furanose derivative **95** in 98% yield.

Smooth conversion of the tosylate **95** to the phenylsulphide **96** (PhSH, DBU)[55] in 61% yield, was followed by treatment of **96** with *N*-chlorosuccinamide in carbon tetrachloride[48] to give the α-chlorosulphide **90**, as a diastereomeric mixture, in what appeared to be a quantitative reaction by t.l.c.. As with α-chlorosulphide 79, crude 90 was reacted directly with silyl enol ether **9** under Lewis acid mediation.

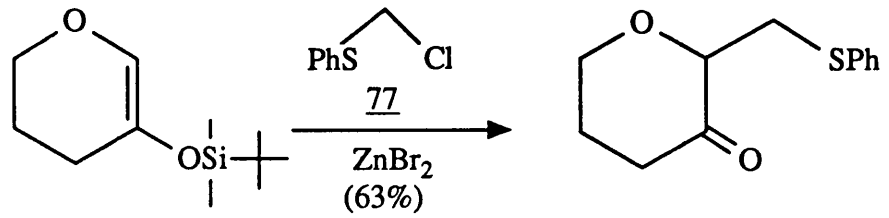
The difference in reactivity of tosylate **92** versus tosylate **95** should be noted. The 3-(*O*-benzyl) derivative **92** reacted with thiophenol and 1,8-diazabicyclo[5.4.0]-undec-7-ene at room temperature over 12h and gave the sulphide **91** in 86% yield. This is in comparison with the 3-(*O*-*tert*-butyldimethylsilyl) derivative **95** which required warming to 50°C for 16h, under the same conditions, to give sulphide **96** in only 61% yield.

This variation in reactivity is presumably a consequence of the greater steric hinderance imparted at C(5), by the *tert*-butyldimethylsilyl group.

2.3d Addition of silyl enol ether 9 to the 5-chloro-5-phenylthio furanose derivatives 79 and 90

The use of α-chlorosulphides for alkylation of silyl enol ethers has been developed, for the most part by Fleming and Paterson[46,56], to the point where it now represents an important regiospecific method for the introduction of thioalkyl substituents α to the carbonyl group of enolisable aldehydes, ketones, carboxylic

Scheme 27



9 97

acids, esters and lactones. The phenylthio group is multipurpose; its presence facilitates the alkylation step, it serves as a functional handle after alkylation and it can be efficiently removed by Raney nickel hydrogenolysis. It was the equivalence of this procedure to a regiospecific alkylation of a ketone (i.e. the ease with which the phenylthio group can be replaced by H) which attracted us to this methodology.

As a preliminary experiment we chose to investigate the reaction of silyl enol ether 9 with chloromethylphenylsulphide 77[57]. Two experiments were conducted in parallel, one with zinc bromide ($ZnBr_2$) and the other with titanium tetrachloride as Lewis acid. This choice of Lewis acids was based on literature precedent[56,46].

The addition of catalytic amounts of zinc bromide to a stirred solution of silyl enol ether 9 and chloromethylphenylsulphide 77 at room temperature gave phenylsulphide 97 in 63% yield.

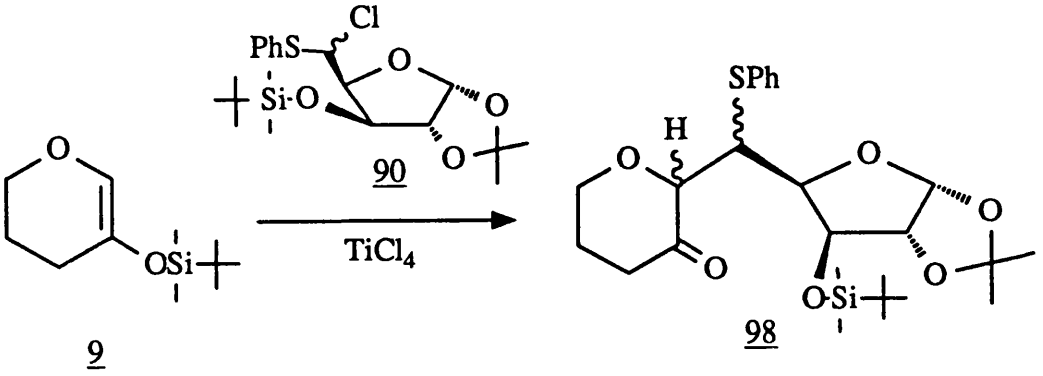
The parallel experiment with titanium tetrachloride was less successful; a similar procedure to that used with zinc bromide, but conducted at -23°C and with one equivalent of titanium tetrachloride, gave only trace amounts of 97 as indicated by t.l.c..

Following this preliminary study we decided to investigate the coupling of silyl enol ether 9 to α-chlorosulphide 90.

Once again, two experiments were conducted in parallel, one with a catalytic amount of zinc bromide and the second with one equivalent of titanium

tetrachloride as the Lewis acid mediator. Reaction of silyl enol ether 9 with α-chlorosulphide 90 and zinc bromide at room temperature, resulted in a complex mixture of reaction products, from which no phenylsulphide **98** was isolated.

Scheme 28



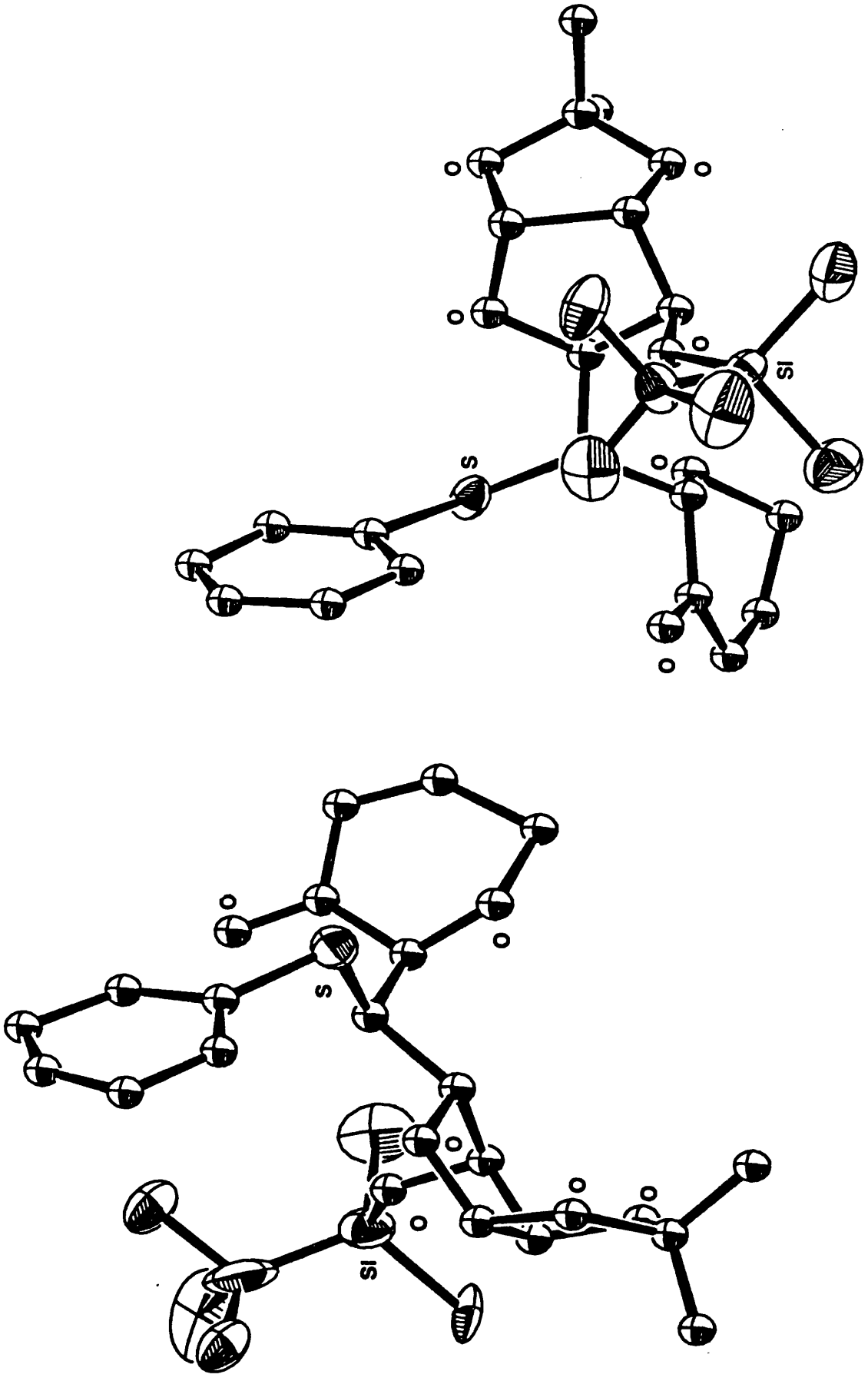
9 98

However, when a solution of silyl enol ether 9 and α-chlorosulphide **90** were treated with titanium tetrachloride (1 equiv.) at -23°C, two chromatographically separable components resulted in approximately equal amounts. Isolation of these two components revealed that the first was a single isomer of the phenylsulphide adduct **98a**. The second component, **98b**, was a mixture of another of the four possible phenylsulphide adducts (cf. Scheme 15) and a trace of impurity which could not be removed by flash chromatography.

When this reaction was repeated at -78°C the combined yield was improved from 25% to 70%. The relative amount of **98a** to **98b** was also increased, from approximately 1:1 to 3:1 (note; these ratios are only approximate as the two components could never be completely separated by flash chromatography).

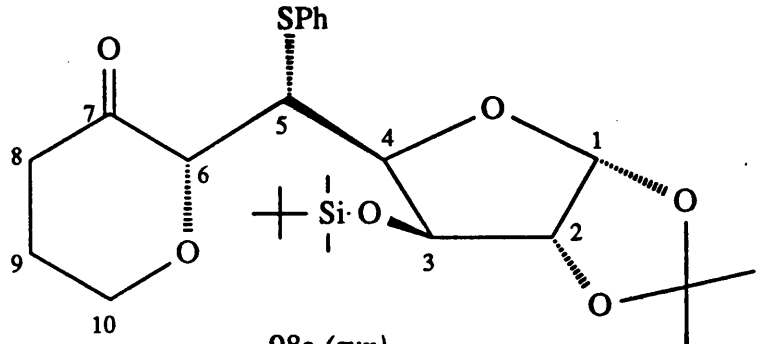
Phenylsulphide **98a** was a crystalline solid and recrystallisation from petrol (b.p. 60-80°C) gave crystals suitable for X-ray analysis. The unit cell contained two

Figure 6



conformations of the same enantiomer and their ORTEP diagrams can be seen in Figure 6.

Scheme 29



98a *(syn)*

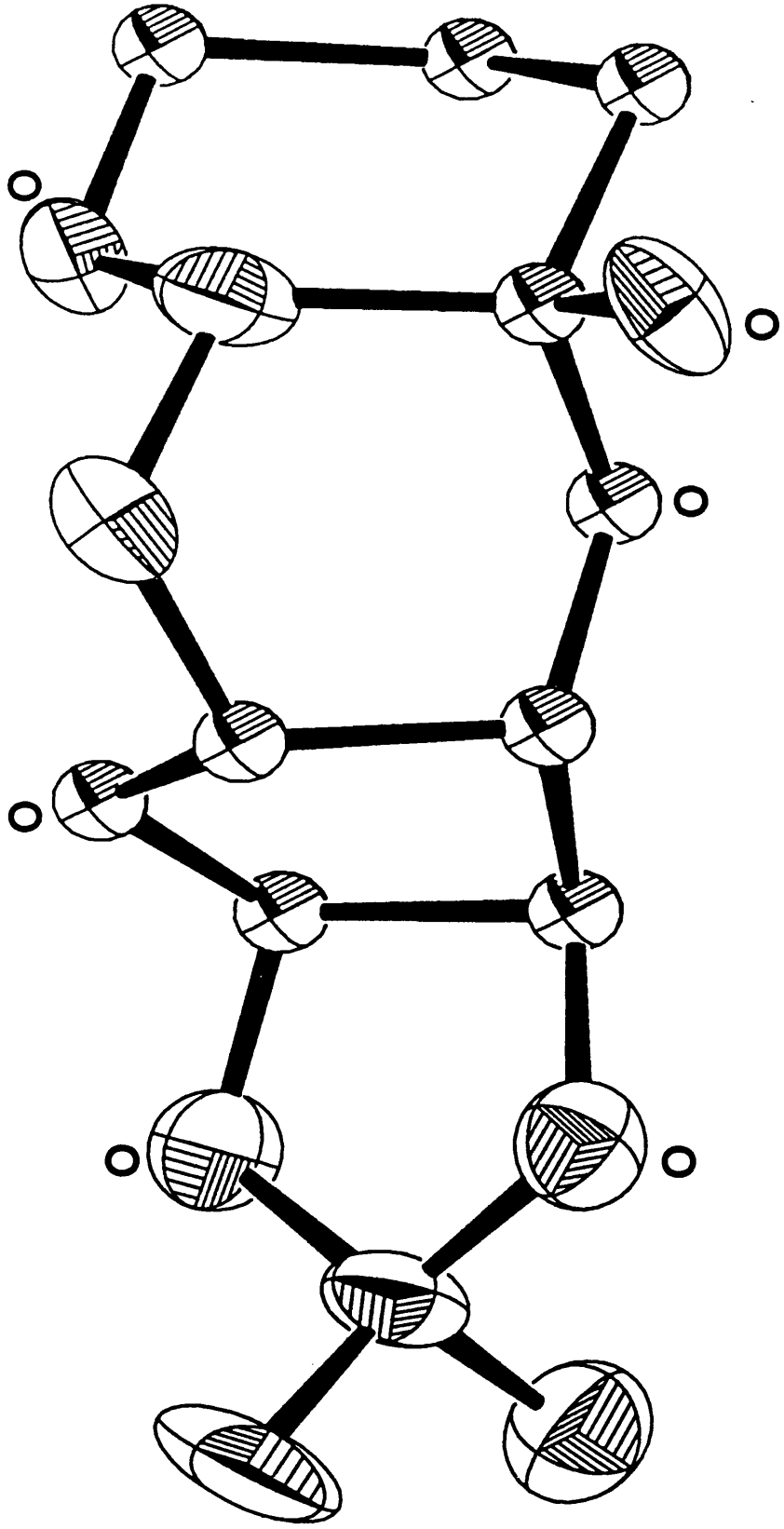
When depicted in the standard aldol notation, as in Scheme 29, it can be seen that the stereochemistry of the created chiral centres, C(5) and C(6), is *syn*.

Scrutiny of **98a** reveals that the stereochemistry at C(6) is the opposite to that present in both the herbicidins and the proposed structures of ketols **86a** and **86b**. Deprotection of the C(3) hydroxyl group and reduction of the C(5) phenylsulphide moiety of **98a** should then provide access to the C(6) epimer of the desired tricycle **89** (cf. Scheme 24).

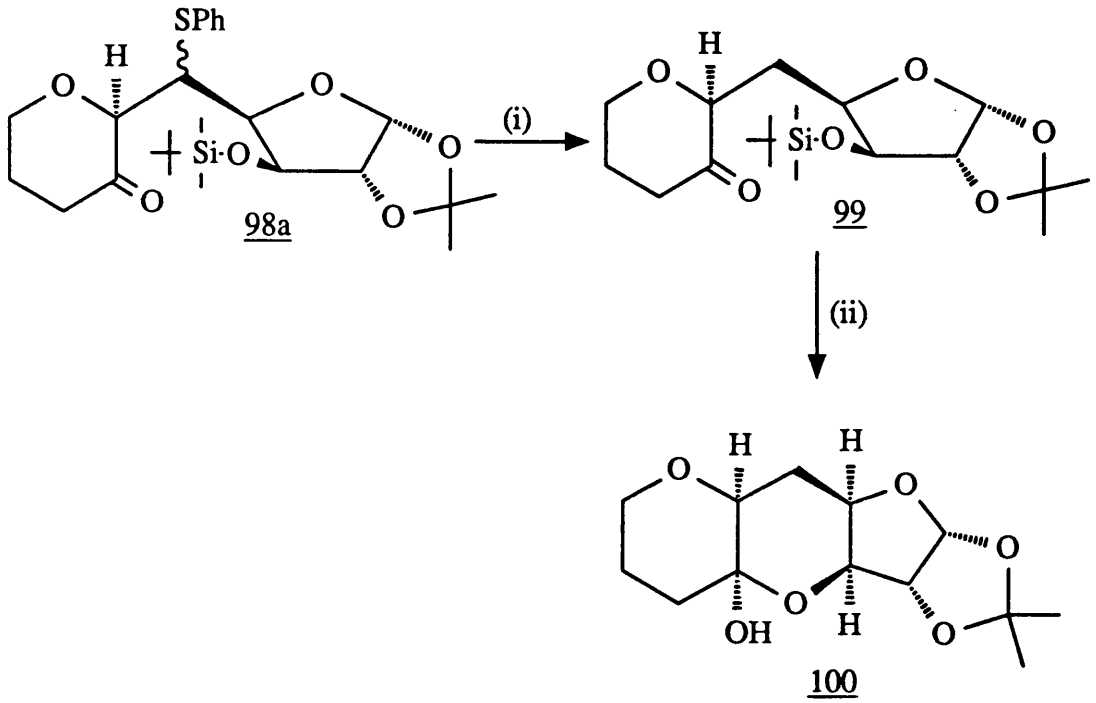
Treatment of phenylsulphide adduct **98a** with freshly prepared W-2-Raney nickel[58] gave the bridged furo-pyran-3-one **99** in 40% yield. This product was then dissolved in dry tetrahydrofuran and treated with tetra-*n*-butylammonium fluoride (TBAF) at -23°C to furnish the tricycle **100** as a colourless crystalline solid in 94% yield. Recrystallisation from petrol (b.p. 60-80°C)/diethyl ether afforded crystals suitable for X-ray crystallograhic analysis. The resulting ORTEP diagram is shown in Figure 7.

As predicted, tricycle **100** is the epimer at C(6) of the herbicidin skeleton. However, the stereochemistry of C(7)OH is correct. Presumably the conformation at this centre is again controlled by the anomeric effect[51].

Figure 7



Scheme 30



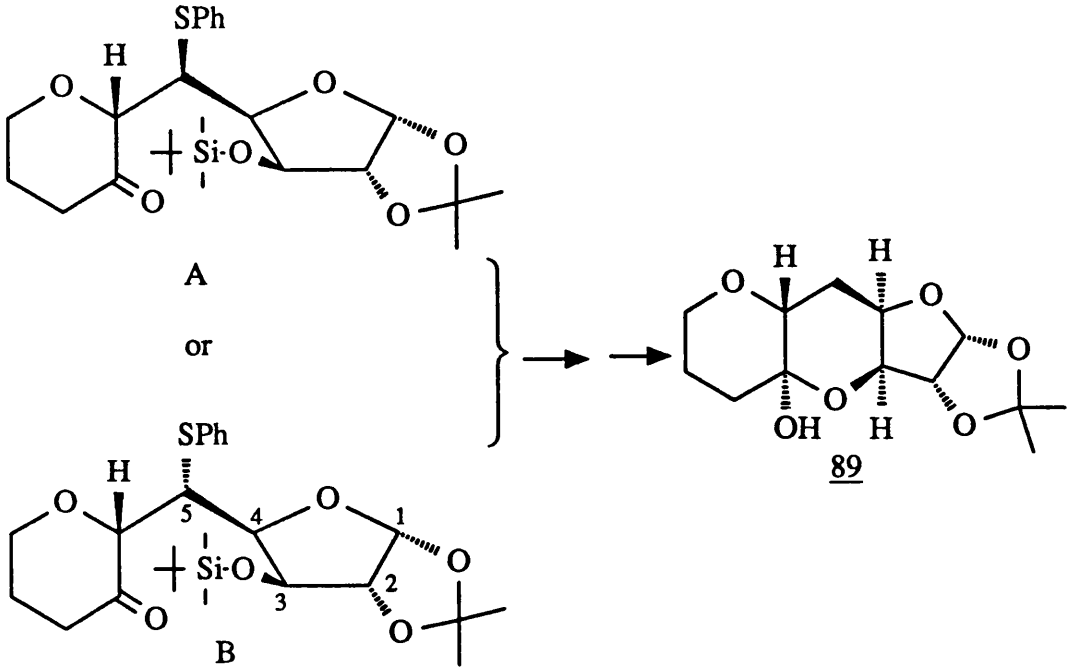
Reagents (i) Raney Ni (40%); (ii) TBAF (94%).

Tricycle **100** was found to be different spectroscopically to the tricycle **89**, derived by deoxygenation of **86b** (Scheme 24). As the only previously undefined stereocentre in **89** was C(6) [C(7) presumed to be controlled by the anomeric effect], then by deduction one would expect the stereochemistry of tricycle **89** to be that already proposed in Scheme 24.

As the second component of the addition reaction of Scheme 28, phenylsulphide **98b** was an oil, no evidence could be obtained about its stereochemistry.

However, treatment of phenylsulphide **98b** with W-2-Raney nickel followed by tetra-*n*-butylammonium fluoride as above, gave a tricyclic compound in an overall yield of 25%. The ^1H n.m.r. data of this tricycle was found to be identical to that of tricycle **89**. This would suggest that phenylsulphide **98b** was one of the two diastereomers indicated in Scheme 31.

Scheme 31



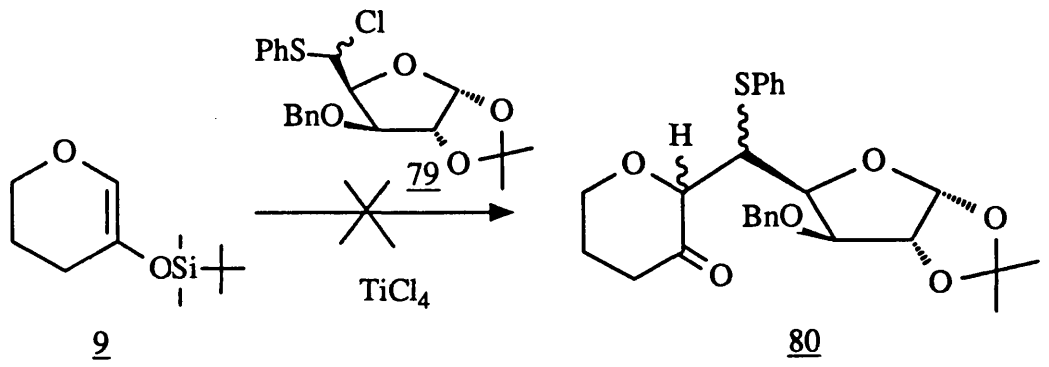
Component 98b

One might speculate that phenylsulphide **98b** has the stereochemistry of isomer B, Scheme 31; i.e. with the same stereochemistry at C(5) as sulphide **98a**. The reasoning behind this speculation is that one face of the intermediate sulphonium ion is expected to be hindered by the sterically demanding *tert*-butyldimethylsilyl group. The two stereoisomers produced are, therefore, assumed to be stereoselective at the C(5) centre; i.e. the difference in stereochemistry arises from the two reactive faces of the silyl enol ether **9**.

Further to our studies with the 3-(*O*-*tert*-butyldimethylsilyl) furanose derivative **90**, we decided to investigate the efficiency of using the 3-(*O*-benzyl) equivalent **79** in a coupling reaction with silyl enol ether **9**.

Initial attempts to perform the reaction shown in Scheme 32 at -78°C gave only starting α-chlorosulphide **79** as product. Repeating the reaction at -23°C, however, resulted in formation of a new compound which was shown by full spectroscopic

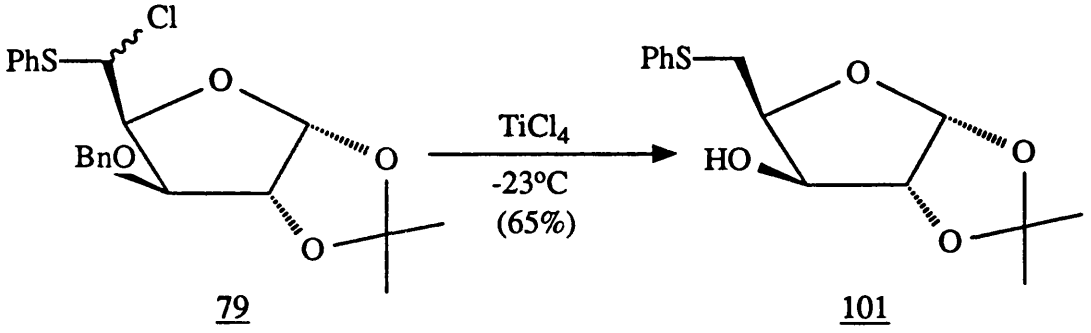
Scheme 32



9 80

and elemental analysis to be the phenylsulphide **101** (65%).

Scheme 33



79 101

Formation of phenylsulphide **101** when the reaction was conducted without silyl enol ether **9**, confirmed that **9** played no role in the reaction of Scheme 33. In order to propose a mechanism for this reaction it was clearly necessary to determine the fate of the benzyl protecting group of **79**.

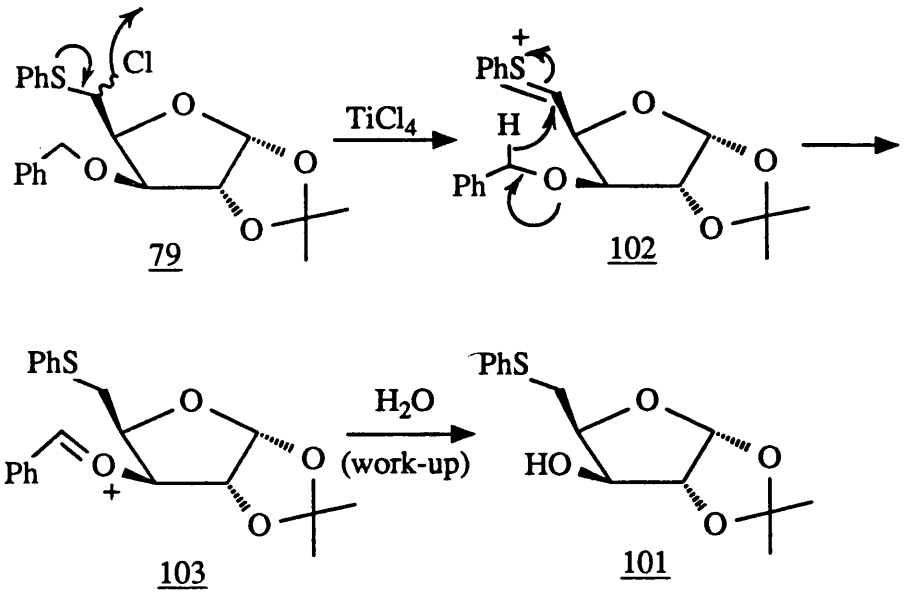
T.l.c. and ^{1}H n.m.r. indicated that benzaldehyde was present in the crude product of the experiment conducted without silyl enol ether **9**. This was confirmed

by the preparation of a 2,4-dinitrophenylhydrazone[32], from the same crude product, which was totally indistinguishable from an authentic sample of benzaldehyde 2,4-dinitrophenylhydrazone.

It would therefore appear that the benzylic carbon is being oxidised, and the C(5) position of the furanose derivative **79** reduced, during the course of the reaction of Scheme 33.

Based on this experimental evidence we propose the mechanism of Scheme 34.

Scheme 34

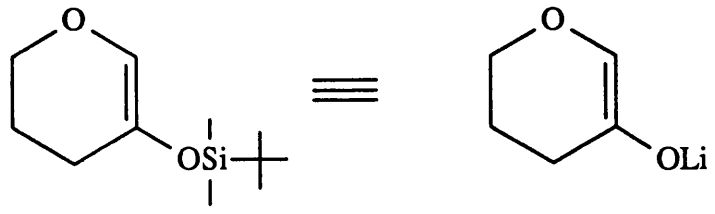


The driving force behind the reaction is presumably the greater stability of the oxonium ion **103** relative to the sulphonium ion **102**.

This 1,5-hydride shift is not without precedent, as Martin[59] has postulated a similar rearrangement in the Lewis acid mediated reactions of other benzylated sugars. Hydride shifts onto α-chlorosulphides have also been reported[60].

2.3e Summary

It has been shown that the silyl enol ether **9** can be used, under Lewis acid mediation, as an equivalent of the regiospecific enolate **10**.



9 **10**

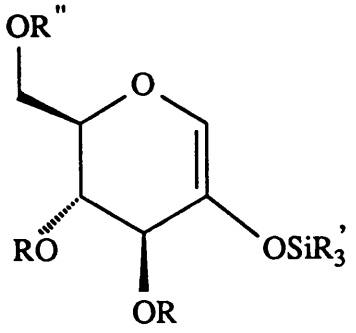
Reaction of silyl enol ether **9** with the furanose aldehyde **63** was a stereoselective process, with only two of four possible diastereomers isolated when either tin tetrachloride or titanium tetrachloride were used to mediate the reaction. Conversion of one of the resultant aldol adducts **85a/b** to an analogue of the carbohydrate portion of the herbicidins **76**, via deprotection and deoxygenation, was possible. However, removal of what appeared to be a sterically hindered hydroxyl group in a second aldol product proved difficult.

Stereoselectivity was also observed when silyl enol ether **9** was reacted with α-chlorosulphide **90** and $TiCl_4$. This to our knowledge is the first example of a stereoselective Lewis acid mediated reaction of a silyl enol ether with an α-chlorosulphide.

Conversion of the sulphide adducts **98**, to the simple herbicidin analogues **76**, was convenient and applicable to both stereoisomers of **98**.

The ultimate aim of this project was to develop chemistry which would provide access to the herbicidins. The above Lewis acid mediated chemistry of silyl enol ether **9** has provided access, via two routes, to simple analogues of the carbohydrate portion of the herbicidins. It is therefore predicted, that the use of similar

chemistry on fully substituted carbohydrate derived silyl enol ethers such as **6**, should provide an entry into the herbicidins. Work in that direction is currently underway.



6

3. EXPERIMENTAL

3. EXPERIMENTAL

INSTRUMENTATION AND EXPERIMENTAL TECHNIQUES

Infrared spectra were recorded in the range 4000-600cm^{-1} using a Perkin-Elmer 1310 grating spectrophotometer and peaks are reported (ν_{max}) in wave numbers (cm^{-1}). Spectra of liquid samples were taken as thin films, or as solutions in chloroform ($CHCl_3$). Spectra of solid samples were taken in chloroform solution, unless otherwise stated.

Routine mass spectra from both electron ionisation (E.I.) and chemical ionisation (C.I.), and high resolution accurate mass determinations were recorded with a VG Analytical 7070E instrument with a VG 2000 data system. Unless otherwise stated the data provided is that from electron ionisation and was produced with an ionising potential of 70eV. Chemical ionisation was conducted with either isobutane or ammonia as reagent gas. Where possible, the molecular ion peak ($M^{+}\cdot$) and base peak are indicated, as are all sizeable fragmentations with assignments.

Proton magnetic resonance (H^1 n.m.r.) spectra were recorded at 60MHz on Hitachi Perkin-Elmer high resolution R-23B and Varian Anaspect EM-360 spectrometers, at 270MHz on a JEOL GNM GX FT 270 spectrometer, at 360MHz on a Bruker EM360 spectrometer (Wellcome Laboratories, Beckenham, Kent) and at 400MHz on a Bruker 400 spectrometer using the SERC facility at Warwick University. ^{13}C n.m.r. spectra were recorded on the JEOL GNM GX FT 270, Bruker EM360 and Bruker 400 spectrometers. ^{1}H and ^{13}C n.m.r. spectra were recorded, unless otherwise noted, in $CDCl_3$, and are expressed in parts per million (δ) downfield from internal tetramethylsilane. Multiplicities are given as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m).

Melting points (m.p.) were determined on commercially available apparatus

(Gallenkamp), and are uncorrected. Elemental microanalyses were carried out using a Carlo Erba 1106 Elemental Analyser.

For experimental procedures of a general nature, a complete general description is given and subsequent details for actual examples include quantities of reagent, yield, and characterisation details.

Thin layer chromatography (t.l.c.) was used extensively as a qualitative guide during reactions and for assessing the purity of compounds. Merck DC-alufolien Kieselgel 60 F_{254} sheets containing fluorescent indicator were used for this purpose. Visualisation of reaction components was achieved by illumination under short wavelength (254 nm) ultraviolet light (when possible), and developing with a 7% (W/V) methanol solution of *dodeca*-molybdophosphoric acid (PMA) followed by warming of the t.l.c. plate.

Unless otherwise stated, petroleum refers to petroleum spirit with boiling point range 60-80°C. This was distilled before use as eluant in column chromatography.

Medium pressure flash column chromatography was routinely employed using Kieselgel 60 (Merck 9385) and 60H silica gel (Merck 7736) for reaction component separations. A pressure gradient was developed using a small, commercially available hand bellow (Gallenkamp). In all cases, columns were prepared in petroleum, and chromatography was carried out with petroleum as the initial eluant, then eluting with ethyl acetate-petroleum mixtures of steadily increasing polarity. Material to be chromatographed was pre-adsorbed onto the column support and applied as a thin layer to the top of the column.

In those cases where reduced pressure distillation was difficult, if not destructive of the higher boiling compounds, or when column chromatography was particularly difficult, analytically pure samples were obtained by employing preparative, centrifugally accelerated, thin-layer radial chromatography (Model 7924 Chromatotron). Absorbent layers (silica gel PF_{254} type 60 TLC from Merck (7749)) coated on circular glass plates were used for large sample loadings of up to

300mg total sample.

Tetrahydrofuran (THF) was pre-dried over sodium wire, then refluxed over sodium benzophenone ketyl under dry nitrogen until anhydrous. This was re-distilled immediately prior to use.

Glassware used for water sensitive reactions was baked in an oven at 120°C for approximately 12h, and allowed to cool in a desiccator over $CaCl_2$. Flasks and stirring bars were, however, additionally flame dried under dry nitrogen.

In all experiments, the excess solvent was evaporated with a Büchi rotary evaporator using a water aspirator at room temperature to avoid unnecessary heating. All yields quoted are of purified products, and are uncorrected.

All other general reagents and solvents were purified and dried when required, using the methods described in D.D. Perrin, W.L.F. Armarego and D.R. Perrin, "Purification of Laboratory Chemicals", 2nd Edn., Pergamon Press, Oxford, 1980.

2D Homonuclear shift-correlated spectra for ^1H couplings using the COSY microprogram have been used extensively throughout, when proton assignments were unclear by simple ^1H n.m.r.

For a brief description of the systematic numbering used herein see the Numbering Conventions section at the beginning of this thesis.

5-(O-*Benzyl*)-3,4-*dihydro*-2(H)-*pyran*(34)

Methane sulphonyl chloride (0.35g, 3.1mmol) was added dropwise to a solution of 3-(*O*-benzyl)tetrahydropyran-2-ol (**33a**) (508mg, 2.4mmol) and triethylamine (2.5g, 25mmol) in dry chloroform (20ml) cooled to 0°C under nitrogen. The mixture was allowed to warm to room temperature and after 45min complete conversion to the mesylate was observed by t.l.c. (followed by formation of (**32a**), methanol quench). After heating under reflux for 5h the resulting brown solution was cooled to room temperature and washed with water (2 x 10ml) and saturated aqueous copper sulphate (10ml). Drying (Na_2SO_4) was followed by evaporation to give a brown oil which was chromatographed on silica to give the *enol ether* (34) as a clear colourless oil (306mg, 66%), b.p. 110-115°C, 0.7mmHg (Kugelrohr); R_f 0.8 (ethyl acetate:petrol, 3:7); (Found: M^+, 190.0988. $C_{12}H_{14}O_2$ requires M, 190.0993); ν_{max} (liq film) 2910, 2850, 1660(w), 1440 and 1360cm^{-1}; δ(270MHz, $CDCl_3$) 1.85-1.94 (2H,m,C(3)Hs), 2.30 (2H,td,J=6.5,1.5Hz, C(4)Hs), 3.85(2H,dd, J=6,4.5Hz,C(2)Hs), 4.63(2H,s,O$\underline{CH_2}$Ph), 6.30(1H,t,J=1.5Hz,C(6)H), 6.29-7.35 (5H, m,$CH_2\underline{Ph}$); *m/z* 190(M^+,13%), 91(100).

5-(O-*Methyl*)-3,4-*dihydro*-2(H)-*pyran*(35)

Methane sulphonyl chloride (1.12g, 9.8mmol) was added dropwise to a solution of 3-(*O*-methyl)tetrahydropyran-2-ol (**33b**) (990mg, 7.5mmol) and triethylamine (2.9g,28.7mmol) in dry chloroform (40ml) cooled to 0°C under nitrogen. The mixture was allowed to warm to room temperature and after 15min complete conversion to the mesylate was observed by t.l.c. (followed by formation of (**32b**), methanol quench). After heating under reflux for 3h the resulting brown solution was cooled to room temperature before diluting with diethyl ether (100ml) and washing with water (100ml) and saturated aqueous copper sulphate (100ml). Drying

(Na_2SO_4) was followed by careful removal of solvent using a Vigreux column to give a brown liquid which was passed down an alumina (neutral) column (Petroleum ether b.p. 30-40°C:diethyl ether, 9:1) to give the *methyl enol ether* (35), after careful removal of solvent using a Vigreux column, as a clear colourless oil (638mg,75%), b.p. 110-115°C, 760mmHg (Kugelrohr); R_f 0.82 (ethyl acetate:petrol, 3:7); (Found: M^+, 114.066. $C_6H_{10}O_2$ requires M, 114.068); ν_{max} (liq film) 3100, 2915, 2825, 1440, 1368, 1125cm^{-1}; δ (270MHz, $CDCl_3$) 1.89(2H,m,C(3)Hs), 2.17 (2H,t,J= 6.5Hz,C(4)Hs), 3.47(3H,s,$OC\underline{H}_3$), 3.82(2H,t,J=4Hz,C(2)Hs), 6.18 (1H,s, C(6)H); *m/z* 114(M^+,64%), 99(M^+- CH_3,8), 86(M^+- C_2H_4,38), 85(21), 57(64), 56(100).

5-[O-(1-*Phenyl*-3-*buten*-1-*yl*)]-3,4-*dihydro*-2(H)-*pyran* (38)

tert-Butyllithium (0.35ml, 1.7M in pentane, 0.6mmol) was added dropwise to a solution of 5-(*O*-benzyl)-3,4-dihydro-2(*H*)-pyran(34) (100mg, 0.53mmol) in dry tetrahydrofuran (2ml) at -78°C under nitrogen. The resulting clear yellow solution was then allowed to warm to 0°C for 30min when it had developed a clear brick red colour. After recooling to -78°C allyl bromide (129mg, 1.1mmol) was added and the resulting clear colourless solution stirred for 15min before the reaction mixture was quenched with saturated aqeous ammonium chloride (2ml). Extraction of the resulting emulsion with ethyl acetate (3x2ml) followed by drying (Na_2SO_4) and evaporation of the solvents gave a clear colourless oil which was purified by radial chromatography (ethyl acetate: petrol, 5:95) to give the *enol ether* (38) as a clear colourless oil (60mg, 50%), R_f 0.66 (ethyl acetate: petrol, 1:9); (Found: M^+,230.1341. $C_{15}H_{18}O_2$ requires M, 230.1305); ν_{max} (liq film) 3060, 3020, 2910, 2840, 1625, 1480, 1435cm^{-1}; δ(270MHz,$CDCl_3$) 1.78-1.86 (2H,m,ring C(3)Hs), 2.05-2.18(2H,m,ring C(4)Hs), 2.44(1H,quin,J=7Hz,C(2)H), 2.63 (1H,quin, J=7Hz,C(2)H), 3.68-3.73(2H,m,ring C(2)Hs), 4.62(1H,dd,J=7.5,5.5Hz,C(1)H), 5.02-

5.09(2H,m,C(4)Hs), 5.78 (1H,ddt,J=17, 10,7Hz, C(3)H), 6.10(1H,t,J=1.5Hz, ring C(6)H), 7.22-7.36(5H,m,Ph); *m/z* 230(M^+,1.5%), 189(M^+-C_3H_5,1), 131(72), 100(100), 91(41).

General procedures for metalation of 5-(*O*-methyl)-3,4-dihydro-*2(H)*-pyran (35)

Procedure A

To a stirred solution of 5-(*O*-methyl)-3,4-dihydro-2(*H*)-pyran(35) (0.5mmol, 1equiv) in dry tetrahydrofuran (~1ml/0.5mmol) at -78°C under nitrogen was added *tert*-butyllithium (1.2equiv). The resulting clear yellow solution was allowed to warm to between -10 and 0°C for 0.5h.

Procedure B

To a stirred solution of 5-(*O*-methyl)-3,4-dihydro-2(*H*)-pyran(35) (0.5mmol, 1equiv) in dry tetrahydrofuran (~1ml/0.5mmol) at 0°C under nitrogen was added *n*-butyllithium (1.2equiv). The resulting clear orange solution was warmed at 50°C for 1h.

1-[5-(O-*Methyl*)-3,4-*dihydro*-2(H)-*pyran*-6-*yl*]*benzyl alcohol* (40)

5-(*O*-Methyl)-3,4-dihydro-2(*H*)-pyran(35) (27mg, 0.23mmol) was metalated as described above, procedure A. The solution of anion was cooled to -78°C and benzaldehyde (50mg, 0.47mmol) was added. After 10min at -78°C reaction was quenched with saturated aqueous ammonium chloride (5ml) and extracted with diethyl ether (4x5ml). Drying (Na_2SO_4) was followed by evaporation to give a clear colourless oil, which was purified by column chromatography on silica to give

the *hydroxybenzyl enol ether* (**40**) as a clear colourless oil (31mg, 60%), R_f 0.27 (ethyl acetate: petrol, 3:7); (Found: M^+,220.1091. $C_{13}H_{16}O_3$ requires M,220.1091); ν_{max} (liq film) 3430(OH), 3045, 3010, 2910, 2830, 1655(w), 1590(w), 1480(w), 1440(w)cm^{-1}; δ(270mHz,$CDCl_3$) 1.85-1.96(2H,m,C(3)Hs), 2.22-2.38 (2H,m, C(4)Hs), 3.00(1H,brs,OH),3.51(3H,s,OCH_3), 3.80-3.92(2H,m,C(2)Hs), 5.68 (1H,s,-CH(OH)Ph), 7.21-7.46 (5H,m,Ph); *m/z* 220 (M^+,100%), 203 (M^+- OH,15), 202 (M^+- H_2O,20), 188 (M^+- CH_4O,34), 187(M^+-CH_5O,57).

1-[5-(O-*Methyl*)-3,4-*dihydro*-2(H)-*pyran*-6-*yl*]*cyclohexan*-1-*ol* (40a)

5-(*O*-Methyl)-3,4-dihydro-2(*H*)-pyran(35) (48mg, 0.42mmol) was metalated as described above, procedure A. The solution of anion was cooled to -78°C when cyclohexanone (83mg, 0.85mmol) was added. The resulting clear red solution was stirred at -78°C for 30min and then quenched with saturated aqueous ammonium chloride (5ml). After allowing the mixture to warm to room temperature it was extracted with dichloromethane (4x5ml). The organics were dried (Na_2SO_4) before evaporating to give a clear colourless oil, which was purified by column chromatography on neutral alumina to give the *hydroxycycloxyl enol ether* (**40a**) as a clear colourless oil (47mg, 53%), R_f 0.6 (ethyl acetate: petrol, 3:7); (Found: M^+,212.1400. $C_{12}H_{20}O_3$ requires M,212.1411); ν_{max} (liq film) 3490(OH), 2920, 2840, 1440(w), 1385(w), 1340(w), 1255(w), 1235(w), 1205, 1140, 1060cm^{-1}; δ (270MHz,$CDCl_3$) 1.56-1.72(10H,m,cyclohexyl), 1.86(2H,quin,J=6.5Hz,C(3)Hs), 2.20 (2H,t,J=6.5Hz,C(4)Hs), 3.51(3H,s,OCH_3),3.78(2H,t,J=5Hz,C(2)Hs), 4.37(1H,brs, OH); *m/z* 212 (M^+,70%), 169 (M^+- C_2H_5O,100).

3-(O-*Methyl*)-4,5-*dihydro*-6(H)-*pyranosonic acid* (**40b**)

5-(*O*-Methyl)-3,4-dihydro-2(*H*)-pyran(35) (43mg, 0.38mmol) was metalated as in

procedure A. The resulting solution of anion was cooled to -78°C when dry carbon dioxide was bubbled through for 30min. After quenching the reaction with saturated aqueous ammonium chloride (3ml) the mixture was allowed to warm to room temperature before saturated aqueous sodium bicarbonate was added until it became basic. The solution was then washed with dichloromethane (4ml), acidified (2N. Hydrochloric acid) and extracted with dichloromethane (4x4ml). After drying (Na_2SO_4) the organic extracts were evaporated to give the *acid* (40b) as a clear colourless oil (28mg, 47%), R_f 0.55(methanol + drop acetic acid); (Found: M^+,158.0561. $C_7H_{10}O_4$ requires M,158.0578); ν_{max} (liq film)3210(OH,br), 1723, (CO,br), 1622(w), 1440, 1400cm^{-1}; δ(60MHz,$CDCl_3$) 1.90-2.20 (2H,m,C(5)Hs), 2.52(2H,t,J=6Hz,C(4)Hs), 3.85(3H,s,OCH_3), 4.00(2H,t,J=5Hz,C(6)Hs), 8.55 (1H, brs,OH); *m/z* 158(M^+,100%), 130(M^+- C_2H_4,8), 113(M^+- CO_2H,8), 85(M^+- $C_3H_5O_2$,20).

5-(O-*Methyl*)-6-[3-(O-*tetrahydropyran-2-yl*)*propan*-1-*yl*]-3,4-*dihydro*-2(H)-*pyran* (43)

5-(*O*-Methyl)-3,4-dihydro-2(*H*)-pyran (104mg, 0.91mmol) (35) was metalated as in procedure B above. The solution of anion was cooled to 0°C, when 1-iodo-3-(tetrahydropyran-2-yloxy)propane[24] (42) (145mg,0.54mmol) in dry tetrahydrofuran (1ml) was added, and then warmed to 50°C. After 1h saturated aqueous ammonium chloride (5ml) was added and the mixture was extracted with dichloromethane (4x5ml). Drying (Na_2SO_4) and evaporation afforded a clear yellow oil which was purified by column chromatography over silica to give the *propyl ether substituted enol ether* (43) as a clear colourless oil (75mg, 54%), R_f 0.7(ethyl acetate:petrol,3:7); (Found: M^+,256.1672. $C_{14}H_{24}O_4$ requires M,256.1674); ν_{max} (liq film) 2925, 2850, 1730(w), 1430(w), 1345(w), 1250(w), 1200, 1150, 1130, 1110, 1070, 1025cm^{-1}; δ(270MHz,$CDCl_3$) 1.56-1.93(10H,m), 2.19-2.37(4H,m), 3.41-3.58(5H,m),

3.77(1H,dt,J=9.5,7Hz), 3.86(2H,t,J=5.5Hz), 3.70-3.95(1H,m), 4.6(1H,dd,J=4.5, 2.5Hz); *m/z* 256(M^+,16%), 172(M^+-C_5H_8O,26), 171(M^+-C_5H_9O,25), 154(M^+-$C_5H_{10}O_2$,31), 139(M^+-$C_6H_{13}O_2$,26), 85(100).

6-[3-(O-*Benzyl)propan*-1-*yl*]-5-(O-*methyl*)-3,4-*dihydro*-2(H)-*pyran* (45)

5-(*O*-Methyl)-3,4-dihydro-2(*H*)-pyran (**35**) (116mg, 1.02mmol) was metalated as in procedure B above. The solution of anion was cooled to 0°C before 3-benzyloxypropyl iodide[26] (**44**) (125mg, 0.45mmol) in dry tetrahydrofuran (1ml) was added, and then the mixture was warmed to 50°C. After 1h saturated aqueous ammonium chloride (2ml) was added and the mixture was extracted with dichloromethane (4x3ml). Drying (Na_2SO_4) and evaporation afforded a clear yellow oil which was purified by column chromatography over silica to give the *propyl ether substituted enol ether* (**45**) as a clear colourless oil (80mg, 65%), R_f 0.75(ethyl acetate:petrol,3:7); (Found: M^+,262.1569. $C_{16}H_{22}O_3$ requires M,262.1569); ν_{max} (liq film) 3090(w), 3065(w), 3035(w), 2930, 2850, 1497, 1455, 1360, 1275, 1255, 1209, 1155, 1090cm^{-1}; δ(270MHz,$CDCl_3$) 1.78(2H,quin,J=7Hz,C(8)Hs), 1.82 -1.91(2H,m,C(3)Hs), 2.17(2H,t,J=6.5Hz,C(7)Hs), 2.28(2H,t,J=7.5Hz,C(4)Hs), 3.45(3H,s,OCH_3), 3.49(2H,t,J=6.5Hz,C(9)Hs), 3.81(2H,t,J=5Hz,C(2)Hs), 4.51(2H,s, $OC\underline{H_2}Ph$), 7.33(5H,s,$OCH_2\underline{Ph}$); MS, NH_3, C.I, *m/z* 280(M^++NH_3,3%), 263(M^++H,61), 262(M^+,21).

5-(O-*Methyl*)-6-[5-(O-*methyl*)-3,4-*dihydro*-2(H)-*pyran*-6-*yl*]-3,4-*dihydro*-2(H)-*pyran* (49)

5-(*O*-Methyl)-3,4-dihydro-2(*H*)-pyran (**35**) (63mg, 0.55mmol) in dry diethyl ether (1ml) was metalated as described in procedure A above. The resulting solution of anion was cooled to -78°C and then transferred via a cannula to a stirred

suspension of cuprous iodide (60mg, 0.3mmol) in dry diethyl ether (1ml) also at -78°C under nitrogen. The resulting white suspension was stirred at -78°C for 1h when it had a grey-black colour. After addition of benzyl bromide (94mg, 0.55mmol) the reaction mixture was stirred at -78°C for 2h and then allowed to warm slowly to room temperature over 1h. Reaction was quenched with saturated aqueous ammonium chloride (5ml) and extracted with dichloromethane (4x5ml). Drying (Na_2SO_4) was followed by evaporation and chromatography over alumina to give the *dimer* (49) as a clear colourless oil (41mg, 66%), R_f 0.44(ethyl acetate:petrol,3:7); δ(60MHz,$CDCl_3$) 1.75-2.45(4H,m,C(3+4)Hs), 3.55(3H,s,OCH_3), 3.95(2H,t,J=5Hz,C(2)Hs).

The lability of this compound made full characterisation difficult. The trazolinedione adduct (51) was therefore prepared.

5-(O-*Methyl*)-6-[5-(O-*methyl*)-3,4-*dihydro*-2(H)-*pyran*-6-*yl*]-3,4-*dihydro*-2(H)-*pyran* (49)

N-*Phenyltriazolinedione adduct* (51)

5-(*O*-Methyl)-3,4-dihydro-2(*H*)-pyran (35) (47mg, 0.42mmol) was metalated as described in procedure A above. The resulting solution of anion was cooled to -78°C, and then transferred via a cannula to a stirred suspension of cuprous iodide (21mg, 0.11mmol) in dry tetrahydrofuran (1ml) also at -78°C under nitrogen. The resulting dark green-black suspension was stirred at -78°C for 0.75h when a new, strongly u.v. active product was observed by t.l.c., R_f 0.49(ethyl acetate:petrol,3:7). After addition of allyl bromide (85.5mg, 0.32mmol) the solution was allowed to warm slowly to room temperature overnight when the product R_f 0.49(ethyl acetate:petrol,3:7) was still the only significant one. Reaction was quenched with saturated aqueous ammonium chloride (5ml) and extracted with dichloromethane (4x5ml). Drying (Na_2SO_4) followed by evaporation, afforded a yellow oil which

was dissolved in dry dichloromethane and cooled to 0°C under nigrogen when a saturated solution of *N*-phenyltriazolinedione in dichloromethane was added dropwise, until the red colour of the dienophile persisted. After stirring at 0°C for 1h the solvent was evaporated and the resulting red solid preadsorbed on silica before purifying on a silica column to give a colourless solid which was recrystallised from ethanol to give the *triazolinedione adduct* (51) as colourless rhombohedral crystals (21mg, 50%, based on CuI) m.p. 173-174.5°C; R_f 0.64(ethyl acetate:petrol,8:2); (Found: C,59.70; H,5.90; N,10.43. $C_{20}H_{23}O_6N_3$ requires C,59.84; H,5.77; N,10.47%); ν_{max} ($CHCl_3$) 1775, 1710, 1600(w), 1400, 1270, 1135, 1095, 1050, 965, 935cm^{-1}; δ(270MHz,$CDCl_3$) 1.73(2H,dm,J=14Hz,C(3)Heq), 1.97(2H,td,J=13,4.5Hz,C(4)Hax), 2.27(2H,qt,J=13,4.5Hz,C(3)Hax), 3.17(2H,dm, J=13.5Hz,C(4)Heq), 3.46(6H,s,OCH_3), 3.76(2H,ddd,J=13.5,11,3Hz,C(2)Hax), 4.33 (2H,ddt,J=11,5,1.5Hz,C(2)Heq), 7.35-7.50(5H,m,N-Ph); MS, Iso-but C.I, *m/z* 402 (M^++H,4%), 401(M^+,31), 370(M^+-C_2H_6,100), 338(M^+-$C_2H_6O_2$,40).

10-(O-*Methyl*)-1,6-*dioxaspiro*[4,5]*decane s* (56a/b)

The tetrahydropyranyl enol ether (43) (93mg, 0.36mmol) was allowed to stand at room temperature for 12h in concentrated hydrochloric acid-H_2O-THF (1:5:20) (2ml), and was then neutralized with saturated aqueous sodium bicarbonate and the bulk of the tetrahydrofuran evaporated. The residue was extracted with dichloromethane (3x3ml) and the combined extracts dried (Na_2SO_4) and evaporated. Thin layer chromatography [silica gel, ethyl acetate:petrol,3:7] showed two major components having R_f 0.51 and 0.46 which were separated using radial chromatography (ethyl acetate: petrol, 1:9) to give the two diastereomeric *spiroketals* (56a/b) as clear colourless oils (35mg, 60%, combined).

(i) The first component (8.9mg, 14%), R_f 0.51(ethyl acetate: petrol, 3:7); (Found: fragment M^+- C_2H_4,144.0787. $C_7H_{12}O_3$ requires M, 144.0786);

$\nu_{max}(CHCl_3)$ 2925, 2870, 1715(w), 1590(w), 1425(w), 1150, 1105, 1085, 1055, 998, 920cm^{-1}; δ_H(400MHz,$CDCl_3$) 1.28-1.35(1H,m,C(8)H), 1.80-1.91(5H,m, C(8)H,C(9)Hax,Heq,C(3)H,C(4)H), 1.97-2.05(2H,m,C(3)H,C(4)H), 3.09-3.10(1H, m,C(10)H), 3.38(3H,s,OCH_3), 3.55-3.60(1H,m,C(7)Heq), 3.83(1H,td,J=11.5,3Hz, C(7)Hax), 3.88-3.99(2H,m,C(2)Hax,Heq); δ_C, H-coupled (C_6D_6) 20.8(t,J=128.5Hz, CH_2), 23.8(t,J=128Hz,CH_2), 24.7(t,J=130Hz,CH_2), 35.5(t,J=132Hz,CH_2), 56.9(qd, J=140,4.5Hz,CH_3), 61.9(t,J=145Hz,CH_2), 68.1(t,J=145.5Hz,CH_2), 79.2(d,J=143Hz, CH); *m/z* 144(M^+-C_2H_4,11,5%); Iso-but C.I, *m/z* 173(M^++H,5%), 172(M^+,2), 171(M^+-H,8), 144(M^+-C_2H_4,51), 141(M^+- OCH_3,100).

(ii) The second component (11.3mg, 18%), R_f 0.46(ethyl acetate: petrol, 3:7); (Found:fragment M^+- C_2H_4,144.0794. $C_7H_{12}O_3$ requires M, 144.0786); ν_{max} ($CHCl_3$) 2930, 1715(w), 1595(w), 1430(w), 1110, 1095, 1060, 1040, 1000, 985, 950, 925cm^{-1}; δ_H(400MHz,$CDCl_3$) 1.64-1.68(3H,m,C(8)Hax,Heq,C(9)Hax), 1.73 (1H,ddd,J=12.5,8.5,4.5Hz,C(4)H), 1.84-1.91(1H,m,C(3)H), 1.96-2.07(2H,m, C(3)H,C(9)Heq), 2.17(1H,ddd,J=12.5,10,7.5Hz,C(4)H), 3.21(1H,dd,J=11,4.5Hz, C(10)Hax), 3.37(3H,s,OCH_3), 3.47-3.52(1H,m,C(7)Heq), 3.73-3.77(1H,m,C(7)Hax), 3.91(1H,td,J=8,7Hz,C(2)H), 3.99(1H,td,J=8,5.5Hz,C(2)H); δ_C, H-coupled (C_6D_6) 24.9(t,J=128Hz,CH_2), 25.2(t,J=132Hz,CH_2), 26.2(t,J=126Hz,CH_2), 34.6(t, J=133Hz,CH_2), 56.4(qd,J=140,5.5Hz,O$\underline{C}H_3$), 61.1(t,J=145Hz,CH_2), 68.7(t, J=146.5Hz,CH_2), 79.8(d,J=141Hz,CH); *m/z* 144(M^+-C_2H_4,18%); Iso-but C.I., *m/z* 173(M^++H,18%), 172(M^+,2), 171(M^+-H,7), 144(M^+-C_2H_4,54), 141(M^+-OCH_3, 100).

(iii) Mixture of components (i)+(ii) (14.8mg, 23%).

2-[3-(O-*Benzyl*)*propan*-1-*yl*]*tetrahydropyran*-3-*one* (62)

To a stirred solution of enol ether (45) (300mg, 1.15mmol) and anhydrous sodium iodide (170mg, 1.13mmol) in dry acetonitrile (1.5ml) at 0°C under nitrogen, was added chlorotrimethylsilane (124mg, 1.15mmol). The resulting deep orange solution containing a white precipitate was stirred at 0°C for 5min after which it was partitioned between 0.5N sodium thiosulphate solution (1.5ml) and dichloromethane (2ml). The aqueous phase was further extracted with dichloromethane (3x2ml) before the combined organic extracts were dried (Na_2SO_4) and evaporated to give an orange oil which was chromatographed over silica to give the *pyranone* (62) as a clear colourless oil (196mg, 70%), R_f 0.43(ethyl acetate:petrol, 3:7); (Found:M^+, 248.1412. $C_{15}H_{20}O_3$ requires M,248.1412); ν_{max} (liq film) 3090(w), 3065(w), 3035(w), 2955, 2930, 2850, 1724(CO), 1498(w), 1456, 1365, 1310(w), 1245(w), 1205(w), 1160(w), 1100cm^{-1}; δ(360MHz, $CDCl_3$) 1.67-1.99(4H,m,C(1+2)Hs), 1.99-2.19(2H,m,ring C(5)Hs), 2.37-2.60(2H,m,ring C(4)Hs), 3.50(2H,t,J=6.5Hz,C(3)Hs), 3.70(1H,td,J=11,4.5Hz,C(6)Hax), 3.78-3.83 (1H,m,ring C(2)H), 4.05(1H,dt,J=11,4.5Hz,C(6)Heq), 4.5(2H,s,$OC\underline{H_2}Ph$), 7.32(5H,s, $OCH_2\underline{Ph}$); *m/z* 248(M^+, 0.34%), 157(M^+- C_7H_7,5), 129(92), 107(47), 91(100).

2-[3-(*O-Benzyl*)*propan*-1-*yl*]*tetrahydropyran*-3-*one. 2,4-Dinitrophenylhydrazone* (62a)

To a suspension of 2,4-dinitrophenylhydrazine (250mg, 1.3mmol) in methanol (5ml) was cautiously added conc sulphuric acid (0.4ml). The warm solution was filtered before the pyranone (62), (50mg, 0.2mmol) in methanol (0.5ml) was added. After 10min the clear orange solution was diluted with water (2-3 drops) when a precipitate formed. After 30min at -10°C the solid was isolated by filtration, and recrystallised from ethanol to give the 2,4-*dinitrophenylhydrazone* (62a) as yellow needles (75mg, 87%), m.p. 103-104°C, R_f 0.66 (methanol: chloroform, 1:19);

(Found: C,58.5; H,5.51; N,12.88. $C_{21}H_{24}O_6N_4$ requires C,58.87; H,5.65; N,13.08%); ν_{max}(KBr disc) 1615(C=N), 1587(NO_2), 1515, 1500, 1420, 1360(w), 1330(NO_2), 1310, 1080, 915, 835(NO_2), 740(NO_2)cm^{-1}; δ(360MHz, C_6D_6), 1.14-1.23(1H,m,ring C(5)Hax), 1.31-1.43(1H,m,ring C(5)Heq), 1.57(1H,ddd, J=16,11, 6.5Hz,ring C(4)Hax), 1.84-2.10(2H,m,C(2)Hs), 2.03-2.14(1H,m,C(1)H), 2.13-2.24 (1H,m,ring C(4)Heq), 2.19-2.30(1H,m,C(1)H), 3.17(1H,ddd, J=12,11,3.5Hz,ring C(6)Hax), 3.52(2H,t,J=5.5Hz, C(3)Hs), 3.67(1H,dt,J=11, 4Hz,ring C(6)Heq), 3.84 (1H,dd,J=6.5,4.5Hz,ring C(2)H), 4.42(2H,s,$OC\underline{H_2}Ph$), 7.16-7.38(5H,m,$OCH_2\underline{Ph}$), 7.53(1H,d,J=10Hz,Ar-ring C(6)H), 7.72(1H,dd,J=10,3Hz,Ar-ring C(5)H), 8.89(1H, d,J=3Hz,Ar-ring C(3)H), 10.69(1H,s,N<u>H</u>); MS,FAB, *m/z* 429 (M^++H,10%).

<u>*Octahydropyrano*[3,2-b]*pyran*-4a-*ols* (29), *cis-trans* mixture</u>

To a solution of pyranone (62) (200mg, 0.8mmol) in absolute ethanol (2ml) was added 10% palladium on charcoal (~25mg). The resulting suspension was stirred vigorously under an atmosphere of hydrogen for 1h when the catalyst was removed by filtration through celite. Evaporation furnished a clear colourless oil which was purified by column chromatography over silica to give a clear colourless oil (110mg, 93%) which slowly crystallised on standing. Recrystallisation from petrol/diethyl ether gave the diastereomeric *pyranopyranols* (29) as rhombohedral crystals, mp 78-80°C, R_f 0.25(ethyl acetate:petrol, 3:7), 0.58(methanol:chloroform, 5;95); (Found: C,60.8; H,9.1. $C_8H_{14}O_3$ requires C,60.7; H,8.9%); (Found: M^+,158.0943. $C_8H_{14}O_3$ requires M,158.0943); ν_{max} (KBr disc) 3400(OH), 2940, 2910, 2865, 2850, 1735(CO,w), 1445, 1435, 1415, 1325, 1290, 1250, 1210, 1160, 1150, 1090, 1040, 1005, 975, 940, 910, 875, 845, 830, 750, 650cm^{-1}; δ_H(360MHz,C_6D_6) 1.08(0.67H,dm,J=10Hz,*cis* C(7)H), 1.21(1H,dm,J=14Hz,*cis* C(3)H,*trans* C(3)H), 1.30-1.35(0.33H,m,*trans* C(7)H), 1.44-1.69(1.67H,m,*cis* C(4)H, *trans* C(4)H,C(7)H,C(8)H), 1.82-2.01(2.33H,m,*cis* C(4)H,C(8)H, *trans* C(3)H,

C(4)H, C(8)H), 2.03-2.30(2H,m,*cis* C(3)H,C(7)H,C(8)H), 3.06-3.23(2H,m, *cis+trans* OH, *cis* C(2)Hax,*trans* C(2)Hax,C(8a)H), 3.36(0.67H,t,J=3Hz, *cis* C(8a)H), 3.47(0.33H,dd,J=12,6Hz, *trans* C(6)Heq), 3.68(0.67H,dm,J=13Hz, *cis* C(6)Heq), 3.81(0.33H,dd,J=12,6Hz, *trans* C(2)Heq), 3.89-4.08(1.67H,m, *cis* C(2)Heq, C(6)Hax, *trans* C(6)Hax); $\delta_C(C_6D_6)$ 20.06(*cis* C(7)), 24.41(*cis* C(3)), 24.46(*trans* C(8)), 24.55(*trans* C(3)), 24.96(*cis* C(8)), 25.77(*trans*(7)), 35.94(*trans* C(4)), 37.73(*cis* C(4)), 60.12(*trans* C(6)), 60.95(*cis* C(6)), 67.54(*cis* C(2)), 68.27(*trans* C(2)), 74.61(*cis* C(8a)), 79.72(*trans* C(8a)), 91.86(*cis* C(4a)), 93.13(*trans* C(4a)); *m/z* 158(M^+, 3%); NH_3 C.I, *m/z* 176(M^++NH_3,3%), 159(M^++H,6), 158(M^+,12), 141(M^+ - OH,100), 140(M^+-H_2O,10).

cis-4a-(O-*Methyl*)*octahydropyrano*[3,2-b]*pyran*(58a) and trans-4a-(O-*Methyl*) *octahydropyrano*[3,2-b]*pyran* (58b)

To a stirred solution of the pyranopyranols (29) (60mg, 0.38mmol) in dry methanol (2ml) at room temperature under nitrogen was added *p*-toluenesulphonic acid (3mg). The resulting clear solution was allowed to stir for 2h when the methanol was removed by evaporation. The residue was taken up in dichloromethane (10ml) and washed with water (2x10ml) before drying (Na_2SO_4) and evaporation to give a mixture of the *cis* and *trans* pyranopyrans (64mg, 98%) as a clear colourless oil. Column chromatography over silica gave two components, the first eluted was cis-4a-(*O-methyl*)*octahydropyrano*[3.2-b]*pyran* (58a) as a clear colourless oil (26mg, 39%), R_f 0.5(ethyl acetate: petrol, 3:7); (Found:M^+,172.1090. $C_9H_{16}O_3$ requires M,172.1098); ν_{max} (liq film) 2940, 2920, 2905, 2850, 1457, 1430, 1377(w), 1355(w), 1345(w), 1333(w), 1319, 1289, 1262, 1218, 1200(w), 1189, 1160, 1145, 1102, 1087, 1070, 1044, 1027, 1001, 964, 939, 900, 873, 837, 748cm^{-1}; δ_H(400MHz, $CDCl_3$) 1.24(1H,m,C(7)Heq), 1.38(1H,td,J=13,5Hz,C(4) Hax), 1.53(1H,m,C(3)Heq), 1.65(1H,m,C(8)Heq), 1.80-2.00(2H,m,C(7)Hax,C(3)Hax),

2.02(1H,m,C(8)Hax), 2.10(1H,m,C(4)Heq), 3.21(3H,s,OCH_3), 3.22(1H,t,J=2.5Hz, C(8a)H), 3.37(1H,ddd,J=12.5,11.5,2Hz,C(2)Hax), 3.61-3.72(2H,m,C(6)Hax,Heq), 3.96(1H,ddt,J=11.5,4.5,1.5Hz,C(2)Heq); δ_C,H-coupled (C_6D_6) 20.3(t,J=127Hz,CH_2), 24.4(t,J=128Hz,CH_2), 25.5(t,J=129Hz,CH_2), 32.5(t,J=127Hz,CH_2), 46.9(q,J=141Hz, CH_3), 61.5(t,J=144Hz,CH_2), 68.0(t,J=141Hz,CH_2), 75.0(d,J=144Hz,CH), 94.8(s,C); *m/z* 172(M^+,67%), 141(M^+- CH_3O,33), 140(M^+- CH_4O,13), 129(61), 112(30), 101(100).

The second component eluted was trans-4a-*(O-methyl)octahydropyrano*[3,2-b]*pyran* (**58b**) as a clear colourless oil (23mg, 34%), R_f 0.3(ethyl acetate:petrol,3:7); (Found:M^+,172.1100. $C_9H_{16}O_3$ requires M,172.1098); ν_{max} (liq film) 2939, 2861, 2839, 1458, 1438, 1370(w), 1329, 1308(w), 1283, 1262, 1210, 1183, 1152, 1122, 1097, 1084, 1058, 1037, 1000(w), 966, 939, 879cm^{-1}; δ_H(400MHz,$CDCl_3$) 1.37 (1H,td,J=13.5,4.5Hz,C(4)Hax), 1.53(1H,m,C(3)Heq), 1.62-1.90(5H,m, C(8)Hax,Heq, C(7)Hax,Heq,C(3)Hax), 2.12(1H,m,C(4)Heq), 3.22(1H,dd,J=11.5,4Hz,C(8a)H), 3.23 (3H,s,$OC\underline{H}_3$), 3.44-3.54(2H,m, C(2)Hax, C(6)Heq), 3.62(1H,ddd,J=12,11,3Hz, C(6)Hax), 3.98(1H,ddt,J=11.5,5,1.5Hz, C(2)Heq); δ_C, H-coupled(C_6D_6) 24.5(t, J=127Hz,CH_2), 24.7(t,J=127Hz,CH_2), 26.4(t,J=127,CH_2), 29.8(t,J=127Hz,CH_2), 46.9(q,J=141Hz,CH_3), 60.6(t,J=143Hz,CH_2), 68.5(t,J=142Hz,CH_2), 80.8(d, J=139Hz,CH), 95.9(s,C); *m/z* 172(M^+, 62%), 141(M^+- OCH_3,38), 140(M^+- CH_4O, 8), 129(61), 112(15), 101(100).

<u>3-(O-*Benzyl*)-5-(3,4-*dihydro*-2(H)-*pyran*-6-*yl*)-1,2-(O-*isopropylidene*)-α-D-*xylose* epimers (66)</u>

To a stirred solution of 3,4-dihydro-2(*H*)-pyran (30) (90mg, 1.1mmol) in dry tetrahydrofuran (1ml) at 0°C under nitrogen was added *n*-butyllithium (0.83ml, 1.6M in pentane, 1.32mmol). The resulting clear solution was then warmed at 50°C for 1h. Cooling to -78°C was followed by addition of the furanose aldehyde (63)

(226mg, 0.8mmol). After stirring for 25min at -78°C reaction was quenched with saturated aqueous ammonium chloride (2ml) and extracted with dichloromethane (4x3ml). Drying (Na_2SO_4) was followed by evaporation to give a clear colourless oil. Thin layer chromatography [silica gel, ethyl acetate:petrol (1:1)] showed two major components having R_f 0.41 and 0.19 which were separated using radial chromatography (ethyl acetate:petrol, 3:7) to give the two diastereomeric *dihydropyran adducts* (66) as clear colourless oils (149mg, 50% combined).

(i) The first component, (76mg, 26%), R_f 0.41(ethyl acetate:petrol, 1:1); (Found:M^+,362.1722. $C_{20}H_{26}O_6$ requires M,362.1728); ν_{max} (liq film) 3495(OH), 3060(w), 3030(w), 2980, 2930, 2860, 1730(w), 1665(w), 1490(w), 1445, 1370, 1345, 1285, 1210, 1160, 1070, 1020, 925, 880, 855, 735, 695cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.32(3H,s,-C$\underline{H}_3$), 1.50(3H,s,-C$\underline{H}_3$), 1.80-1.86(2H,m,C(9)Hs), 2.01-2.07(2H, m,C(8)Hs), 3.18(1H,d,J=8Hz,-O$\underline{H}$), 3.99-4.05(2H,m,C(10)Hs), 4.13(1H,d, J=3Hz,C(3)H), 4.27-4.37(2H,m,C(4)H,C(5)H), 4.55(1H,d part AB_q,J=11.5Hz,-O$C\underline{H}_2$Ph), 4.60(1H,d,J=4Hz,C(2)H), 4.67(1H,d part AB_q,J=11.5Hz,-O$C\underline{H}_2$Ph), 4.88(1H,t,J=3.5Hz,C(7)H), 6.00(1H,d,J=4Hz,C(1)H), 7.34(5H,s,-OCH$_2\underline{Ph}$); *m/z* 362(M^+, 2.5%), 304(M^+- C_3H_6O,1.5), 249(2), 213(1), 168(2), 161(1), 113(20), 91(100).

(ii) The second component (73mg, 24%), R_f 0.19(ethyl acetate:petrol,1:1), gave spectral data similar to component one, however the ^{1} Hn.m.r. indicated that some decomposition had occured.

3-(O-*Benzyl*)-1-(3,4-*dihydro*-2(H)-*pyran*-6-*yl*)*pent*-4-*ene*-1,2-*diols* (69a/b)

To a stirred solution of 3,4-dihydro-2(*H*)-pyran (65) (30) (90mg, 1.1mmol) in dry tetrahydrofuran (1ml) at 0°C under nitrogen was added *n*-butyllithium (0.83ml,

1.6M in pentane, 1.32mmol). The resulting clear solution was warmed at 50°C for 1h then cooled to 20°C and the furanose iodide (**64**) (109mg, 0.28mmol) was added. The addition was accompanied by a short period of effervescence and after a further 10min stirring at 20°C reaction was quenched with saturated aqueous ammonium chloride (2ml) and extracted with dichloromethane (4x5ml). Drying (Na_2SO_4) was followed by evaporation to give a clear colourless oil. Thin layer chromatography [silica gel, ethyl acetate:petrol (3:7)] showed two major new components having R_f 0.33 and 0.26, which were separated using column chromatography on silica to give the two diastereomeric *dihydropyran adducts* (**69a/b**) as clear colourless oils (57mg, 71%, combined).

(i) The first component (20mg, 25%), R_f 0.33(ethyl acetate: petrol, 3:7); ν_{max} (liq film) 3450(OH), 3060(w), 3020(w), 2920, 2860, 1710(w), 1445, 1380, 1270, 1230, 1060, 1025, 990, 925cm^{-1}; δ_H(270MHz, $CDCl_3$) 1.78-1.82(2H,m,ring C(3)Hs), 2.02-2.06(2H,m,ringC(4)Hs), 2.59(1H,d,J=8Hz,C(2)O<u>H</u>, removed by D_2O), 2.98(1H,d,J=8Hz,C(1)O<u>H</u>, removed by D_2O), 3.71(1H,ddd,J=8,6,3Hz,C(2)H), 3.95-4.09(4H,m,ring C(2)Hs,C(1)H,C(3)H), 4.35(1H,d part AB_q,J=11.5Hz,-OC<u>H</u>$_2$Ph), 4.63(1H,d part AB_q,J=11.5Hz,-OC<u>H</u>$_2$Ph), 4.84(1H,t,J=4Hz,ring C(5)H), 5.34(1H,d, J=11Hz, C(5)H), 5.39(1H,d,J=3.5Hz,C(5)H), 5.98(1H,ddd,J=17,10.5,7.5Hz,C(4)H), 7.26-7.35(5H,m,-OCH$_2$<u>Ph</u>); MS, Iso-but C.I, *m/z* 291(M^++H,1%), 273(M^+- OH, 2.5), 255(M^+- O_2H_3,1), 227(1), 217(2.5), 199(2), 181(3.5), 91(100).

(ii) The second component (37mg, 46%), R_f 0.26(ethyl acetate:petrol, 3:7); ν_{max}(liq film) 3440(OH), 3060(w), 3020(w), 2920, 2860, 1665(w), 1380, 1340, 1270, 1230, 1110, 1060, 990, 915cm^{-1}; δ_H(270MHz,$CDCl_3$) 1.73-1.81(2H,m,ringC(3)Hs), 1.99-2.05(2H,m,ringC(4)Hs), 2.78(1H,brs,C(2)O<u>H</u>), 2.92(1H,brs,C(1)OH), 3.73(1H,t,J=4.5Hz,C(2)H), 3.89-4.01(4H,m,ringC(2)Hs,C(1)H, C(3)H), 4.35(1H,d part AB_q,J=11.5Hz,-OC<u>H</u>$_2$Ph), 4.65(1H,d part AB_q,J=11.5Hz,-

$OC\underline{H_2}Ph$), 4.79(1H,t,J=3.5Hz,ring(5)H), 5.36(1H,d,J=10.5Hz,C(5)H), 5.41(1H,d,J=4Hz,C(5)H), 5.90(1H,ddd,J=17,10.5,8Hz,C(4)H), 7.26-7.37(5H,m,-$OCH_2\underline{Ph}$); $\delta_C(CDCl_3)$ 19.8(ring(C4)), 22.3(ring(C3)), 66.2(ring(C2)), 70.3($O\underline{C}H_2Ph$), 71.9(C(1)), 73.7(C(2)), 81.0(C(3)), 97.9(ring(C(5)), 120.0(C(5)), 127.8(Ph), 128.0(Ph), 128.4(Ph), 135.0(C(4)), 137.6(Ph), 152.2(ring(C(6)); MS, Iso-but C.I, *m/z* 291(M^++H,1.3%), 273(M^+- OH,2.5), 255(M^+- O_2H_3,1), 227(1), 217(3), 199(2), 181(4), 91(100).

2-(O-*Benzyl)tetrahydropyran*-3-*ol* (**81**)

To a cold (-10 to -5°C) solution of 3,4-dihydro-2(*H*)-pyran (30) (30g, 357mmol) in distilled benzyl alcohol (350ml, excess), was added *meta*-chloroperoxybenzoic acid (53g, 80%, 250mmol) slowly (~25min). The resulting suspension was allowed to warm slowly to room temperature and then stirred for 12h. Following distillation to remove the excess dihydropyran and benzyl alcohol the reaction mixture was treated with 2N. sodium hydroxide (200ml) and stirred vigorously for 0.5h. Extraction with dichloromethane (4x200ml) was followed by drying (Na_2SO_4), evaporation and column chromatography on silica to give the *tetrahydropyran*-3-*ol* (**81**) as a clear colourless oil (30g, 58%), b.p. 125-130°C, 0.06mmHg; R_f 0.14(ethyl acetate: petrol, 3:7); (Found: C,69.4; H,8.03. $C_{12}H_{16}O_3$ requires C, 69.25; H, 7.69%); ν_{max}(liq film) 3420 (br,OH), 3055, 3020, 2930, 2850, 1490, 1450, 1260, 1200, 1120, 1075, 1035, 985, 960, 900, 870, 735, 695cm^{-1}; δ(270MHz, $CDCl_3$) 1.45-1.62(2H, m, C(5)Hs), 1.68-1.80(1H,m,C(4)H), 1.99-2.08(1H,m,C(4)H), 2.59(1H,d, J=4.5Hz, $O\underline{H}$), 3.44-3.56(2H,m,C(6)Hs), 3.89-3.96(1H,m,C(3)H), 4.37(1H,d,J=5.5Hz,C(2)H), 4.52(1H,d part AB_q,J=11.5Hz,-$OC\underline{H_2}Ph$), 4.85(1H,d part AB_q,J=11.5Hz,-$OC\underline{H_2}Ph$), 7.25-7.37(5H,m,- $OCH_2\underline{Ph}$); MS, NH_3 C.I., *m/z* 226(M^++NH_3,51%), 209(M^+ +H,5), 191(M^+- OH,38).

2-(*O-Benzyl*)-3-(O-tert-*butyldimethylsilyl*)*tetrahydropyran* (**82**)

To a solution of *tert*-butyldimethylsilyl chloride (4.5g, 30mmol) and 1,8-diazabicyclo[5.4.0] undec-7-ene (4.5g, 30mmol) in dry dichloromethane (40ml), at room temperature, was added tetrahydropyranol (**81**) (5.2g, 25mmol) under nitrogen. The resulting clear solution was stirred at room temperature for 12h when it was diluted with dichloromethane (40ml) and washed with water (50ml), 2N. hydrochloric acid (50ml) and saturated aqueous sodium bicarbonate (50ml). Drying (Na_2SO_4) was followed by evaporation to give an oil which was distilled to give the *disubstituted tetrahydropyran* (**82**) as a clear colourless oil (7.5g, 94%), b.p. 151-153°C, 0.05mmHg; R_f 0.66(ethyl acetate: petrol, 3:7); (Found: C,67.00; H,9.69. $C_{18}H_{30}O_3Si$ requires C, 67.08; H, 9.32%); ν_{max}(liq film) 3080, 3050, 3020, 2940, 2910, 2840, 1450, 1385, 1350, 1245, 1195, 1120, 1070, 1030, 1010, 960, 870, 830, 770, 730, 695, 660cm^{-1}; δ(400MHz,$CDCl_3$) 0.00(3H,s,$SiCH_3$), 0.02(3H,s,$SiC\underline{H}_3$), 0.85(9H,s,*t*Bu), 1.39-1.46(1H,m,C(5)H), 1.48-1.56(1H,m,C(5)H), 1.80-1.88(1H,m,C(4)H), 1.90-1.98(1H,m,C(4)H), 3.48(1H,ddd,J=11,6.5, 3.5Hz,C(6)H), 3.57(1H,dt,J=6.5,4Hz,C(3)H), 3.84(1H,ddd,J=11,8,3.5Hz,C(6)H), 4.38(1H,d,J=4.5Hz,C(2)H), 4.51(1H,d part AB_q,J=12Hz,-$OC\underline{H}_2$Ph), 4.80(1H,d part AB_q,J=12Hz,-OCH_2Ph), 7.22-7.36(5H,m,-$OCH_2\underline{Ph}$); MS,Iso-but C.I., *m/z* 321 (M^+- H,1%), 289(1), 265(M^+- *t*Bu,7), 247(1.5), 221(2), 215(M^+- OBn,100).

3-(O-tert-*Butyldimethylsilyl*)*tetrahydropyran*-2-*ols* (**83**)

To a solution of the disubstituted tetrahydropyran (**82**) (1.27g, 3.95mmol) in absolute ethanol (5ml) was added 10% palladium on charcoal (100mg). The resulting suspension was stirred vigorously under an atmosphere of hydrogen for 6h when the catalyst was removed by filtration through celite. Evaporation furnished a clear colourless oil which was purified by column chromatography over silica to

give the *tetrahydropyran-2-ol* (**83**) (diastereomeric mixture) as a clear colourless oil (784mg, 86%), b.p. 125°C, 0.09mmHg (kugelrohr); R_f 0.48(ethyl acetate: petrol, 3:7); (Found: C,56.60; H,10.51. $C_{11}H_{24}O_3Si$ requires C,56.85; H, 10.41%); ν_{max}(liq film) 3390(OH), 2945, 2915, 2880, 2845, 1465, 1440, 1365, 1255, 1200, 1130, 1105, 1060, 1010, 945, 905, 875, 840, 780cm^{-1}; δ(270MHz, $CDCl_3$) 0.09(2.5H,s,SiC$\underline{H}_3$), 0.10(3.5H,s,SiC$\underline{H}_3$), 0.90(3.6H,s,*t*Bu), 0.92(5.4H,s,*t*Bu), 1.44-2.01(4H,m,C(4),C(5)Hs), 3.26(1H,brs,O*H*, removed D_2O), 3.42-3.55(1.2H,m, C(6)Hs), 3.70-3.75(0.8H,m,C(6)Hs), 3.88-3.97(1H,m, C(3)H), 4.57(0.4H,d,J=5.5Hz, C(2)H), 4.81(0.6H,brs,C(2)H); *m/z* 215 (M^+- OH,1%), 203(1), 199(M^+- CH_4O, 1.5), 175(M^+- *t*Bu,18), 157[M^+-(*t*Bu+OH),39], 129(30), 101(34), 83(80), 75(100).

5-(O-tert-*Butyldimethylsilyl*)-3,4-*dihydro*-2(H)-*pyran* (9)

Methane sulphonyl chloride (1.1g, 9.6mmol) was added dropwise to a solution of 3-(*O-tert*-butyldimethylsilyl)tetrahydropyran-2-ol (**83**) (1.1g, 4.7mmol) and triethylamine (2.2g, 21.5mmol) in dry chloroform (10ml) cooled to 0°C under nitrogen. After allowing the solution to come to room temperature for 20min it was heated under reflux for 3h. The resulting brown solution was cooled to room temperature before washing with water (20ml) and 2N hydrochloric acid (10ml). Drying (Na_2SO_4) was followed by evaporation to give a brown oil which was purified by column chromatography on silica (petrol:ethyl acetate, 9.5:0.5) to give the *silyl enol ether* (**9**) as a clear colourless oil (805mg, 80%), b.p. 120°C, 13mmHg, R_f 0.66(ethyl acetate: petrol, 1:3); (Found: M^+,214.1381. $C_{11}H_{22}O_2Si$ requires M, 214.1388); ν_{max}(liq film) 2907, 2820, 1455, 1358, 1250, 1196, 1142, 1075(w), 1042(w), 1001, 927, 896, 870(w), 848, 835, 790(w), 773, 670(w)cm^{-1}; δ(270 MHz, $CDCl_3$) 0.00(6H,s,Si(C$\underline{H}_3$)$_2$), 0.80(9H,s,Si*t*Bu), 1.70-1.78(2H,m,C(3)Hs), 1.98 (2H,td,J=6,1.5Hz,C(4)Hs), 3.66(2H,dd,J=6,4.5Hz,C(2)Hs), 6.17(1H,t,J=1.5Hz,C (6)H); *m/z* 214 (M^+,100%), 157(M+-*t*Bu,43), 129(69), 127(M^+-C_6H_{15},80),

101(30), 75(85), 73(87), 59(52); (Found: C,61.6; H,10.59. $C_{11}H_{22}O_2Si$ requires C, 61.62; H,10.35%).

1-(3-*Oxotetrahydropyran-2-yl)benzyl alcohols* (84)

To a stirring solution of benzaldehyde (42mg,0.4mmol) in dichloromethane (2ml) at -78°C, under nitrogen, was added distilled tin tetrachloride (104mg, 0.4mmol). The resulting colourless complex was stirred for 15min after which silyl enol ether (9) (103mg, 0.48mmol) was added dropwise over 5min. After a further 2h stirring at -78°C reaction was quenched by rapidly injecting saturated aqueous sodium bicarbonate (2ml) before the mixture was allowed to warm to room temperature. Extraction with diethyl ether (2x30ml) was followed by drying (Na_2SO_4), evaporation and column chromatography over silica to give a diastereomeric mixture of *tetrahydropyran-3-ones* (84) as a clear colourless oil (40mg, 49%), R_f 0.2(ethyl acetate: petrol, 1:3); ν_{max}(liq film) 3430(br,OH), 3050(w), 3010(w), 2950, 2910, 2845, 1710(CO), 1490, 1445, 1405, 1320, 1238, 1195, 1155, 1110, 1085, 1025, 980, 955, 910, 855, 800, 755, 700 cm^{-1}; δ(270MHz, $CDCl_3$) 1.97-2.29(2H,m,C(5)H), 2.41-2.67(2H,m,C(4)H), 2.82(0.4H,brs,OH), 3.62 (0.4H,ddd, J=11.5, 10, 3.5Hz,C(6)Hax), 3.70(0.6H,ddd,J=11.5,10,3.5Hz,C(6)Hax), 3.93(0.4H,d, J=7.5Hz, C(2)H), 4.00(0.4H,dddd,J=10,6.5,3.0,1.5Hz,C(6)Heq), 4.04(0.6H,d, J=3.5Hz, C(2)H), 4.14(0.6H,dddd,J=11.5,5.5,3.5,1.5Hz,C(6)Heq), 4.92(0.4H,d, J=7.5Hz,-CH(OH)Ph), 5.22(0.6H,d,J=3.5Hz,-C*H*(OH)Ph), 7.25-7.43(5H,m,Ph); MS, Iso-but C.I., *m/z* 207 (M^++H,1%), 206(M^+,1.5), 205(M^+-H,2.5), 189(M^+-OH,100), 107(M^+-$C_5H_7O_2$,36), 100(M^+-C_7H_6O,57).

3-(O-*Benzyl*)-1,2-(O-*isopropylidene*)-5-(3-*oxotetrahydropyran*-2-*yl*)-α-D-*xylose* derivatives (85a/b)

To a stirred solution of the furanose aldehyde (**63**) (95mg, 0.34mmol) in dichloromethane (2ml) at -78°C, under nitrogen, was added distilled tin tetrachloride (44mg, 2.23mmol). The resulting clear colourless solution was stirred for 15min after which time silyl enol ether (**9**) (89mg, 0.42mmol) was added dropwise over 5min. After a further 45min the reaction was quenched by rapidly injecting saturated aqueous sodium bicarbonate (2ml). The mixture was then allowed to warm to room temperature before extracting with diethyl ether (2x30ml) and drying over Na_2SO_4. Evaporation and column chromatography on silica then furnished the diastereomeric mixture of *xylose derivatives* (**85a/b**) as a viscous, colourless oil (45mg, 35%), R_f 0.55(ethyl acetate); $\nu_{max}(CHCl_3)$ 3480(OH), 2925, 2850, 1720(CO), 1600(w), 1370, 1160, 1070, 1010, 850 cm^{-1}; δ(270MHz, $CDCl_3$) 1.32(1.5H,s,C$\underline{H}_3$), 1.34(1.5H,s,C$\underline{H}_3$), 1.50(3H,s,C$\underline{H}_3$), 1.96-2.22(2H,m,C(9)Hs), 2.39-2.51(1H,m,C(8)H), 2.55-2.66(1H,m,C(8)H), 3.64-3.85(2H,m,C(10)Hax,C(3)H), 4.05-4.16(3H,m,C(10)Heq,C(6)H,O$\underline{H}$), 4.28-4.34(1H,m,C(4)H), 4.44-4.72(4H,m,C(5)H,C(2)H,-OC$\underline{H}_2$Ph), 5.91(0.5H,d,J=4Hz,C(1)H), 5.99(0.5H,d,J=4Hz,C(1)H), 7.30-7.42(5H,m,-OCH$_2\underline{Ph}$); MS, Iso-but C.I., *m/z* 361 (M^+- OH,2.5%), 321(M^+-C_3H_5O,2.5), 320(M^+- C_3H_6O,2.0), 303(M^+- $C_3H_7O_2$,10.5), 279(M^+- $C_5H_7O_2$, 6.5), 91(100).

(2R,3R)-2,3-O-*Isopropylideneperhydrofuro*[3,2-b]*pyrano*[2,3-e]*pyran*-4a,9-*diols* (86a) and (86b)

To a solution of xylose derivatives (**85a/b**) (20mg,0.05mmol) in absolute ethanol (0.5ml) was added 10% palladium on charcoal (2mg). The resulting suspension was stirred vigorously under an atmosphere of hydrogen for 24h when the catalyst was

removed by filtration through celite. Evaporation furnished an oil which was purified by column chromatography on silica to give two major components.

(i) The first component, *furo-pyrano-pyran* (**86a**), crystallised on standing and was recrystallised from a tetrahydrofuran/petrol mixture to give colourless needles (2.6mg, 20%), m.p. 197-199°C (sealed tube), R_f 0.75(ethyl acetate), 0.24(ethyl acetate: petrol, 1:1); (Found:C,54.40; H,7.17. $C_{13}H_{20}O_7$ requires C,54.16; H,6.99%); $\nu_{max}(CHCl_3)$ 3440(OH), 2915, 2845, 1720(w,CO), 1595, 1370, 1340, 1310, 1075, 1008, 968, 858 cm^{-1}; δ(400MHz, $CDCl_3$) 1.29(3H,s,C$\underline{H}_3$), 1.45-1.58(2H,m,C(9)Heq,C(8)Hax), 1.48(3H,s,C$\underline{H}_3$), 1.82(1H,dm,J=13Hz,C(8)Heq), 2.08(1H,qt,J=13.5,4.5Hz,C(9)Hax), 3.34(1H,d,J=3Hz,C(6)H), 3.52(1H,ddd,J=13.5, 11,2Hz,C(10)Hax), 4.02(1H,dd,J=11.5,4.5Hz,C(10)Heq), 4.16(1H,brs,C(5)O$\underline{H}$), 4.29(1H,brs,C(5)H), 4.34(1H,t,J=2.5Hz,C(4)H), 4.46(1H,d,J=1.5Hz,C(3)H), 4.56(1H, d,J=3.5Hz,C(2)H), 5.53(1H,brs,C(7)O$\underline{H}$), 5.87(1H,d,J=3.5Hz,C(1)H); MS,Iso-but C.I., *m/z* 289 (M^++H,8%), 271(M^+- OH,100), 253(M^+- H_3O_2,25), 213(M^+- $C_3H_7O_2$,43), 195(M^+- $C_3H_9O_3$,21).

(ii) The second component, *furo-pyrano-pyran* (**86b**), also crystallised on standing and was recrystallised from a tetrahydrofuran/petrol mixture to give colourless needles (4.1mg, 30%), m.p. 190-193°C (decomposed), R_f 0.31(ethyl acetate), 0.05(ethyl acetate: petrol, 1:1); (Found:C,54.40; H,7.31. $C_{13}H_{20}O_7$ requires C,54.16; H,6.99); $\nu_{max}(CHCl_3)$ 3350(OH), 2910, 2845, 1740(w,CO), 1595, 1370, 1085, 1000, 972, 940, 903 cm^{-1}; δ(400MHz, $CDCl_3$,2 drops C_2D_6OS) 1.21(3H,s,C$\underline{H}_3$), 1.39(3H,s,CH_3), 1.48-1.57(2H,m,C(8)Hax,C(9)Heq), 1.75-1.79 (1H,m,C(8)Heq), 1.84-1.97(1H,m,C(9)Hax), 3.25(1H,d,J=10Hz,C(6) H), 3.36(1H, ddd,J=12.5, 11.5, 2.5Hz,C(10)Hax), 3.96(1H,dd,J=11.5,5Hz,C(10)Heq), 4.03(1H,dd, J=10,4Hz,C(5)H), 4.30(1H,d,J=2Hz,C(3)H),3.40(1H,dd,J=4,2Hz,C(4)H), 4.45(1H,d, J=3.5Hz,C(2)H), 5.82(1H,d,J=3.5Hz,C(1)H); MS,Iso-but C.I., *m/z* 289 (M^++H,7%),

271(M^+- OH,100), 253(M^+- H_3O_2,89), 213(M^+- $C_3H_7O_2$,38), 195 (M^+- $C_3H_9O_3$,23).

3-(O-*Benzyl*)-1,2-(O-*isopropylidene*)-5-(3-*oxotetrahydropyran*-2-*yl*)-α-D-*xylose* derivatives (**85c**) and (**85d**)

To a stirred solution of the furanose aldehyde (**63**) (98.8mg, 0.4mmol) in dichloromethane (0.5ml) at -78°C, under nitrogen, was added titanium tetrachloride (0.4ml, 1M. in dichloromethane, 0.4mmol) dropwise. The resulting orange-red solution was stirred for 15min after which time silyl enol ether (**9**) (92.6mg, 0.4mmol) was added dropwise over 5min. After a further 15min the reaction was quenched by rapidly injecting saturated aqueous sodium bicarbonate (5ml). The mixture was then allowed to warm to room temperature before extracting with dichloromethane (3x6ml) and drying over Na_2SO_4. Evaporation furnished an oil which was purified by column chromatography on silica to give two major components.

(i) The first component, *xylose derivative* (**85c**), was a viscous, colourless oil (28.7mg, 19%), R_f 0.30(ethyl acetate: petrol,1:1); (Found:Fragment, M^+- C_3H_6O, 320.1251. $C_{17}H_{20}O_6$ requires M,320.1258); ν_{max}(liq film) 3450(OH), 3050(w), 3020(w), 2970, 2940, 2910, 2850, 1715(CO), 1445, 1370, 1245, 1205, 1155, 1075, 1015, 855, 780, 725, 690 cm^{-1}; δ(270MHz, $CDCl_3$) 1.34(3H,s,$C\underline{H}_3$), 1.50 (3H,s,CH_3), 1.96-2.19(2H,m,C(9)Hs), 2.39-2.64(2H,m,C(8)Hs), 3.69(1H,ddd,J=11.5, 9.5, 4.0Hz,C(10)Hax), 3.78(1H,d,J=5.5Hz,C(3)H), 4.05-4.13 (1H,m,C(10)Heq), 4.08 (1H,d,J=4Hz,C(6)H), 4.31(1H,t,J=5.5Hz,C(4)H), 4.43 (1H,dd,J=5.5,4Hz,C(5)H), 4.49(1H,d part AB_q,J=12Hz,-O$C\underline{H}_2$Ph), 4.67 (1H,dd,J=4,1Hz,C(2)H), 4.71(1H,d part AB_q,J=12Hz,-O$C\underline{H}_2$Ph), 5.99(1H,d,J =4Hz,C(1)H), 7.26-7.38(5H,m,-O$CH_2\underline{Ph}$); *m/z* 320(M^+- C_3H_6O,1%), 91(100);Iso-but C.I., *m/z* 379(M^++H,0.5%), 378(M^+,

0.5), 377(M^+- H,2), 361(M^+- OH,1), 321(M^+- C_3H_5O,2), 320(M^+- C_3H_6O,1.5), 91(100).

(ii) The second component, *xylose derivative* (**85d**), was also a viscous, colourless oil (31.8mg, 21%), R_f 0.20(ethyl acetate: petrol,1:1); (Found: Fragment, M^+- C_3H_6O, 320.1218. $C_{17}H_{20}O_6$ requires M,320.1258); ν_{max}(liq film) 3430(OH), 3050(w), 3020(w), 2970, 2920, 2840, 1715(CO), 1490, 1445, 1370, 1310, 1250, 1205, 1160, 1070, 1015, 890, 855, 790, 735, 700cm^{-1}; δ(270MHz, $CDCl_3$) 1.34(3H,s,C$\underline{H}_3$), 1.50(3H,s,C$\underline{H}_3$), 1.82-1.95(1H,m,C(9)H), 2.07-2.37(2H,m, C(9)H,C(8)H), 2.45-2.64(2H,m,C(8)H,O$\underline{H}$), 3.31(1H,ddd,J=11.5, 10, 4Hz, C(10) Hax), 3.40(1H,d,J=2.5Hz,C(6)H), 3.92(1H,d,J=3.5Hz,C(3)H), 4.04(1H,dt, J=11.5, 5Hz,C(10)Heq), 4.35(1H,dd,J=7.5,3.5Hz,C(4)H), 4.37(1H,d part AB_q, J=12Hz,-OC$\underline{H}_2$Ph), 4.42-4.49(1H,m,C(5)H), 4.67(1H,d, J=4Hz, C(2)H), 4.72(1H,d part AB_q, J=12Hz,-OC$\underline{H}_2$Ph), 5.99(1H,d,J =4Hz,C(1)H), 7.26-7.36(5H,m,-OCH$_2$C$\underline{H}$); *m/z* 320 (M^+- C_3H_6O,1.5%), 91(100);Iso-but C.I., *m/z* 379 (M^++H,1%), 361(M^+- OH,1.5), 321(M^+- C_3H_5O,1.5), 320(M^+- C_3H_6O,2.5), 91(100).

(2R,3R)-2,3-O-*Isopropylideneperhydrofuro*[3,2-b]*pyrano*[2,3-e]*pyran*-4a,9-*diol* (**86c**)

To a solution of xylose derivative (**85c**) (65.6mg, 0.17mmol) in absolute ethanol (2ml) was added 10% palladium on charcoal (10mg). The resulting suspension was stirred vigorously under an atmosphere of hydrogen for 12h when the catalyst was removed by filtration through celite. Evaporation furnished a colourless solid which crystallised from a tetrahydrofuran/petrol mixture as colourless needles of the *diol* (**86c**) (31mg, 65%), m.p. 197-199°C (sealed tube), R_f=0.6(ethyl acetate). The spectroscopic data were identical with those of diol (**86a**).

(2R,3R)-2,3-O-*Isopropylideneperhydrofuro*[3,2-b]*pyrano*[2,3-e]*pyran*-4a,9-*diol* (86d)

To a solution of xylose derivative (**85d**) (67mg, 0.18mmol) in absolute ethanol (2ml) was added 10% palladium on charcoal (10mg). The resulting suspension was stirred vigorously under an atmosphere of hydrogen for 48h when the catalyst was removed by filtration through celite. Evaporation furnished a colourless oil which was purified by column chromatography over silica to give the *diol* (**86d**) as a colourless solid (30mg, 56%). Recrystallisation from toluene gave colourless needles m.p. 170-173°C (sealed tube), R_f 0.42(ethyl acetate : petrol, 3:1); (Found:fragment; M^+- CH_3, 273.0954. $C_{12}H_{17}O_7$ requires M,273.0972); $\nu_{max}(CHCl_3)$ 3360(OH), 2920, 2850, 1375, 1140, 1060, 1010, 965 cm^{-1}; δ(270MHz, $CDCl_3$, 2 drops C_2D_6OS) 1.15(3H,s,C$\underline{H}_3$), 1.25-1.31(1H,m,C(9)Heq), 1.32(3H,s,C$\underline{H}_3$), 1.47(1H,td, J=12,4Hz,C(8)Hax), 1.60(1H,qt,J =12,4Hz,C(9)Hax), 1.81 (1H,dm,J=12Hz, C(8) Heq), 3.13(1H,td,J=11.5,2Hz,C(10)Hax), 3.15(1H,dd,J= 2.5,1Hz,C(6)H), 3.80(1H, dm,J=11.5Hz,C(10)Heq), 3.88(1H,t,J=2Hz,C(5)H), 3.98(1H,t,J=2Hz,C(4)H), 4.29 (1H,d,J=2.5Hz,C(3)H), 4.43(1H,d,J=4Hz,C(2) H), 5.76(1H,d,J=4Hz,C(1)H); *m/z* 273 (M^+- CH_3,9%); Iso-but C.I., *m/z* 289 (M^++H,6%), 271(M^+- OH,100), 253 (M^+- H_3O_2,20), 213(M^+- $C_3H_7O_2$,35), 195(M^+-$C_3H_9O_3$,16).

(2R,3R)-2,3-(O-*Isopropylidene*)-9-(O-*thiocarbonylimidazole*)*perhydrofuro*[3,2-b]*pyrano*[2,3-e]*pyran*-4a-*ol* (88)

To a stirred solution of furo-pyrano-pyran (**86b**) (16.7mg, 0.042mmol) in dry *N,N*-dimethylformamide (0.5ml) at room temperature (19°C), under nitrogen, was added thiocarbonyldiimidazole (14.9mg, 0.08mmol). The resulting clear yellow solution was stirred at room temperature for 16h after which time the *N,N*-dimethylformamide was removed under high vacuum. The yellow oil was then dissolved in dichloromethane (3ml) before washing with water (4x2ml) and drying

over Na_2SO_4. Evaporation was followed by purification via column chromatography on silica to give the *thiocarbonylimidazole pyranol* (**88**) as a clear colourless oil (9.3mg, 55%), R_f 0.5(ethyl acetate); δ(270MHz,$CDCl_3$) 1.31 (3H,s,C<u>H</u>$_3$), 1.47(3H,s,C<u>H</u>$_3$), 1.70-2.33(4H,m,C(8)Hs,C(9)Hs), 3.11(1H,brs,O<u>H</u>), 3.48(1H,td,J=12,2Hz,C(10)Hax), 3.84(1H,d,J=10Hz,C(6)H), 4.05(1H,dd,J=12, 4.5Hz,C(10)Heq), 4.54(1H,d,J=2Hz,C(3)H), 4.59(1H,d,J=4Hz,C(2)H), 4.80(1H,dd, J=4,2Hz,C(4)H), 5.96(1H,d,J=4Hz,C(1)H), 6.09(1H,dd,J=10,4Hz,C(5)H), 7.03(1H,s, Im), 7.67(1H,s,Im), 8.37(1H,s,Im).

<u>(2R,3R)-2,3-O-*Isopropylideneperhydrofuro*[3,2-b]*pyrano*[2,3-e]*pyran*-4a-*ol* (89)</u>

A mixture of thiocarbonylimidazole derivative (**88**) (9.3mg, 0.023mmol), tributyltin hydride (20mg, 0.069mmol) and azobisisobutyronitrile (~2mg,cat) were heated at reflux in toluene (1ml), under nitrogen, for 1h. After cooling, the mixture was evaporated to dryness. The resulting oil was taken up in diethyl ether (1ml) and then saturated aqueous potassium fluoride (2ml) was added before the mixture was stirred vigorously for 12h. After separating off the organic phase the aqueous was extracted with dichloromethane (3x2ml). The combined organic extracts were then dried over Na_2SO_4, evaporated, and purified by column chromatography over silica to give the *furo-pyrano-pyranol* (**89**) as a viscous, colourless oil (2mg, 30%), R_f 0.3(ethyl acetate: petrol, 1:1); ν_{max}($CHCl_3$) 3400(OH), 2910, 2845, 1715(w, CO), 1370, 1160, 1135, 1075, 1010, 975, 950 cm^{-1}; δ(270MHz, $CDCl_3$) 1.31(3H, s,C<u>H</u>$_3$), 1.49(3H,s,C<u>H</u>$_3$), 1.61-2.19(6H,m,C(5)Hs,C(8)Hs,C(9)Hs), 3.48(1H,td,J=12, 2.5Hz, C(10)Hax), 3.52(1H,dd,J=12,5Hz,C(6)H), 3.98(1H,dd,J=12,5Hz,C(10)Heq), 4.30(1H,d,J=2Hz,C(3)H), 4.41(1H,dd,J=5.5,2Hz,C(4)H), 4.52(1H,d,J=4Hz,C(2)H), 5.88(1H,d,J=4Hz,C(1)H); MS, Iso-but C.I., *m/z* 273(M^++H,25%), 257(M^+- CH_3, 44), 255(M^+- OH,100), 215(M^+- C_3H_5O,40), 197(M^+- $C_3H_7O_2$,23).

3-O-*Benzyl-5-deoxy-1,2-O-isopropylidene-5-phenylthio-α-D-xylofuranose* (91)

To a stirred emulsion of 1,8-diazabicyclo[5.4.0]undec-7-ene (218mg,1.43mmol) and thiophenol (158mg, 1.43mmol) in dry benzene (5ml) at room temperature, under nitrogen, was added tosylate (92) (622mg, 1.43mmol). The resulting mixture was stirred for 12h after which time it was diluted with dichloromethane (30ml) and washed with 2N hydrochloric acid (20ml) and saturated aqueous sodium bicarbonate (20ml). Drying (Na_2SO_4) was followed by evaporation and column chromatography, on silica, to give the *xylose derivative* (91) as a clear colourless oil (460mg, 86%), R_f 0.2(ethyl acetate: petrol, 1:9); (Found: M^+,372.1404. $C_{21}H_{24}O_4S$ requires M,372.1393); ν_{max}(liq film) 3040(w), 3010(w), 2960, 2910, 1570, 1470, 1440, 1425, 1360, 1335(w), 1305(w), 1280(w), 1240, 1200, 1150, 1060, 1010, 945, 870, 845, 805(w), 725, 685 cm^{-1}; δ(270MHz, $CDCl_3$) 1.29(3H,s, $C\underline{H}_3$), 1.42(3H,s,$C\underline{H}_3$), 3.24(2H,d,J=7.5Hz,C(5)Hs), 3.99(1H,d,J=3Hz,C(3)H), 4.33(1H,td,J=7.5,3Hz,C(4)H), 4.44(1H,d part AB_q,J=11.5Hz,-$OC\underline{H}_2$Ph), 4.59(1H,d, J=4Hz,C(2)H), 4.63(1H,d part AB_q,J=11.5Hz,-$OC\underline{H}_2$Ph), 5.91(1H,d, J=4Hz,C(1)H), 7.40-7.15(10H, m,-S$\underline{Ph}$,-$OCH_2\underline{Ph}$); *m/z* 372(M^+,8.5%), 91(100).

3-O-*Benzyl-5-chloro-5-deoxy-1,2-O-isopropylidene-5-phenylthio-α-D-xylofuranose* (79)

To a stirred solution of the sulphide (91) (252mg, 0.68mmol) in dry carbon tetrachloride (1.5ml), under an atmosphere of nitrogen, was added *N*-chlorosuccinamide (95mg, 0.7mmol). The resulting suspension was stirred for 4h at room temperature after which time it was filtered and evaporated to give the crude *α-chlorosulphide* (79) (distereomeric mixture) as a clear yellow oil (273mg, 99%), R_f 0.58, 0.54(ethyl acetate: petrol, 3:7); MS, Iso-but C.I., *m/z* 409[M^++H, 1.5%,(Cl,37)], 408[M^+,2,(Cl,37)], 407[M^++H,4,(Cl,35)], 406[M^+,4.5,(Cl,35)].

This crude product was reacted without further purification or characterisation.

3-(O-tert-*Butyldimethylsilyl*)-1,2-O-*isopropylidene*-5-*toluene*-p-*sulphonyl*-α-D-*xylofuranose* (95)

To a stirred solution of tosylate (94) (1g, 2.9mmol) and *tert*-butyldimethylsilyl chloride (0.44g, 2.9mmol) in dry dichloromethane (25ml) at room temperature, under nitrogen, was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.53g, 3.5mmol). The resulting clear colourless solution was stirred at room temperature for 17h after which time it was diluted with dichloromethane (20ml) and then washed with water (40ml), 2N hydrochloric acid (40ml) and saturated aqueous sodium bicarbonate (40ml). Drying (Na_2SO_4) was followed by evaporation and purification by column chromatography, on silica to give the 3-O-tert-*butylidimethylsilyl*-α-D-*xylofuranose* (95) as a clear colourless oil (1.28g, 98%), R_f 0.47(ethyl acetate: petrol, 1:3); (Found: C,54.90; H,7.70. $C_{21}H_{34}O_7SSi$ requires C,54.99; H,7.47%); ν_{max}(liq film) 3040(w), 3020(w), 2970, 2940, 2910, 2870, 2840, 1595, 1455, 1360, 1305, 1285, 1250, 1215, 1175, 1118, 1075, 1010, 980, 940, 835, 775, 675cm^{-1}; δ(270MHz, $CDCl_3$) 0.07(3H,s,SiC$\underline{H}_3$), 0.11(3H,s,SiC$\underline{H}_3$), 0.85(9H,s, SitBu), 1.29(3H,s,C$\underline{H}_3$), 1.44(3H,s,C$\underline{H}_3$), 2.45(3H,s,PhC$\underline{H}_3$), 4.07-4.29(4H,m, C(3)H,C(4)H,C(5)Hs), 4.32(1H,d,J=3.5Hz,C(2)H), 5.84(1H,d,J=3.5Hz,C(1)H), 7.34(2H,d part AB_q, J=8Hz,Ph), 7.80(2H,d part AB_q,J=8Hz,Ph); MS, Iso-but C.I., *m/z* 459(M^++H, 61%), 401(M^+- *t*Bu,16), 287(M^+- OTos,10), 229(48).

3-(O-tert-*Butyldimethylsilyl*)-5-*deoxy*-1,2-O-*isopropylidene*-5-*phenylthio*-α-D-*xylofuranose* (96)

To a stirred emulsion of 1,8-diazabicyclo[5.4.0]undec-7-ene (178mg,1.2mmol) and thiophenol (129mg, 1.2mmol) in dry benzene (5ml) at room temperature, under nitrogen, was added tosylate (95) (535mg, 1.2mmol). The resulting mixture was heated at 50°C for 16h after which time it was diluted with dichloromethane

(20ml) and washed with 2N hydrochloric acid (15ml) and saturated aqueous sodium bicarbonate (15ml). Drying (Na_2SO_4) was followed by evaporation and column chromatography, on silica, to give the *5-phenylthio-α-D-xylofuranose* (**96**) as a clear colourless oil (288mg, 61%), R_f 0.45(ethyl acetate: petrol, 1:9); (Found: M^+,396.1800. $C_{20}H_{32}O_4SSi$ requires M,396.1789); ν_{max}(liq film) 3050(w), 2910, 2870, 2830, 1580, 1460, 1435, 1375, 1315, 1290, 1250, 1215, 1165, 1135, 1080, 1015, 960, 940, 835, 780, 740, 690cm^{-1}; δ(270MHz, $CDCl_3$) 0.16(3H,s,SiC<u>H</u>$_3$), 0.17(3H,s,SiC<u>H</u>$_3$), 0.91(9H,s,Si*t*<u>Bu</u>), 1.30(3H,s,C<u>H</u>$_3$), 1.40(3H,s,C<u>H</u>$_3$), 3.10(1H, ddd,J=13,10,1Hz,C(5)H), 3.22(1H,dd,J=13,5Hz,C(5)H), 4.23-4.29(2H,m,C(3)H, C(4)H), 4.38(1H,d,J=3.5Hz,C(2)H), 5.90(1H,d,J=3.5,Hz,C(1)H), 7.16-7.40(5H,m, -S<u>Ph</u>); *m/z* 396(M^+,9%), 381(M^+ - CH_3,5), 339(M^+ - *t*Bu,100).

<u>3-(O-tert-*Butyldimethylsilyl*)-5-*chloro*-5-*deoxy*-1,2-O-*isopropylidene*-5-*phenylthio*-α-D-*xylofuranose* (90)</u>

To a stirred solution of the sulphide (**96**) (422mg, 1.1mmol) in dry carbon tetrachloride (5ml), under an atmosphere of nitrogen, was added *N*-chlorosuccinamide (186mg, 1.4mmol). The resulting suspension was stirred for 12h at room temperature after which time it was filtered and evaporated to give the crude *α-chlorosulphide* (90) (diastereomeric mixture) as a clear yellow oil (468mg, 99%), R_f 0.61, 0.57(ethyl acetate: petrol, 1:3).

This crude product was reacted without further purification or characterisation.

<u>2-*Phenylthiomethyltetrahydropyran*-3-*one* (97)</u>

To a stirred solution of silyl enol ether (**9**) (90mg, 0.4mmol) and chloromethylphenylsulphide (77)[57] (81mg, 0.51mmol) in dichloromethane (1ml) at room temperature, under nitrogen, was added anhydrous zinc bromide (~10mg,cat).

The resulting colourless suspension was stirred at room temperature for 0.5h when it was diluted with dichloromethane (5ml) and washed with water (5ml). Drying (Na_2SO_4) was followed by evaporation and column chromatography on silica to give the *phenylthiomethylpyranone* (97) as a clear colourless oil (56mg, 63%), R_f 0.3(ethyl acetate: petrol, 1:3); (Found:M^+,222.0712. $C_{12}H_{14}O_2S$ requires M,222.0712); ν_{max}(liq film) 3040, 2940, 2920, 2840, 1710, 1580, 1475, 1435, 1410, 1300, 1240, 1150, 1100, 1020, 955, 740, 690 cm^{-1}; δ(270MHz,$CDCl_3$) 2.01-2.29(2H,m,C(5)Hs), 2.41-2.68(2H,m,C(4)Hs), 3.11(1H,dd,J=13.5,8Hz,-$C\underline{H}_2$SPh), 3.49(1H,dd,J=13.5, 4Hz,-$C\underline{H}_2$SPh), 3.77(1H,ddd,J=12, 10.5,3.5Hz, C(6) Hax), 4.01(1H,dd,J=8,4Hz,C(2)H), 4.13(1H,dddd,J=12,5,3,1.5Hz,C(6)Heq), 7.16-7.42(5H,m,-S$\underline{Ph}$); *m/z* 222(M^+,36%), 123(M^+- $C_5O_2H_7$,100), 71(27).

3-(O-tert-*Butyldimethylsilyl*)-5-*deoxy*-1,2-O-*isopropylidene*-5-(3-*oxotetrahydropyran*-2-yl)-5-*phenylthio*-α-D-*xylofuranose* derivatives (98a) and (98b)

To a stirred solution of the crude α-chlorosulphide (90) (542mg, 1.26mmol) and silyl enol ether (9) (204mg, 0.95mmol) in dichloromethane (5ml) at -78°C, under nitrogen, was added titanium tetrachloride (1ml, 1M in dichloromethane, 1mmol). After 0.5h reaction was quenched by rapidly injecting saturated aqueous sodium bicarbonate (8ml). The resulting emulsion was allowed to warm to room temperature before extracting with dichloromethane (4x15ml), drying over Na_2SO_4 and column chromatography on silica to give the two 5-*tetrahydropyranone xylofuranose* derivatives (98a) and (98b) (333.4mg, 70%, combined) in three components.

(i) The first component (98a) was a colourless solid which recrystallised from petrol as clear colourless rhombic crystals (73.8mg, 16%), m.p. 128-130°C; R_f 0.38(ethyl acetate: petrol, 1:3); (Found: C,60.60;H,7.78. $C_{25}H_{38}O_6SSi$ requires C,60.69;H,7.74%); ν_{max}($CHCl_3$) 2920, 2840, 1710(CO), 1110, 1070, 1010

cm^{-1}; δ(270MHz,$CDCl_3$) 0.05(3H,s,SiC$\underline{H}_3$), 0.14(3H,s,SiC$\underline{H}_3$), 0.85-0.92(9H,m,Si $\underline{t}$Bu), 1.30(3H,s,C$\underline{H}_3$), 1.47(3H,s,C$\underline{H}_3$), 1.90-2.03(1H,m,C(9)H), 2.26-2.37 (1H,m, C(9)H), 2.44(1H,dd,J=9,7Hz,C(8)H), 2.68-2.80(1H,m,C(8) H), 3.63 (1H,ddd,J=11.5, 10.5,4Hz,C(10)Hax), 3.98(1H,dd,J=10.5,2Hz,C(5)H), 4.04(1H, brs,C(6)H), 4.10-4.18 (2H,m including d, J=2.5Hz,C(10)Heq,C(3)H), 4.38(1H, d,J= 3.5Hz,C(2)H), 4.43 (1H,dd,J=10.5,2.5Hz,C(4)H), 5.84(1H,d,J=3.5Hz,C(1)H), 7.15-7.26(3H,m,-S$\underline{Ph}$), 7.51-7.55(2H,m,-S$\underline{Ph}$); *m/z* 494(M^+,20%), 479(M^+- CH_3,4), 437(M^+- *t*Bu,3), 395 (M^+- $C_5H_7O_2$,13), 337(57).

(ii) The second component (**98b**) was a colourless oil (60mg, 13%), R_f 0.33(ethyl acetate: petrol, 1:3); (Found: M^+,494.2127. $C_{25}H_{38}O_6SSi$ requires M,494.2156); ν_{max}(liq film) 3060, 2960, 2930, 2850, 1720(CO), 1580(w), 1455, 1435, 1370, 1250, 1215, 1160, 1110, 1075, 1015, 945, 910, 830, 770 cm^{-1}; δ(270MHz,$CDCl_3$) 0.08(3H,s,SiC$\underline{H}_3$), 0.14(3H,s,SiC$\underline{H}_3$), 0.88(9H,s,Si$\underline{t}$Bu), 1.31(3H, s,C$\underline{H}_3$), 1.49(3H,s,C$\underline{H}_3$), 1.96-2.07(1H,m,C(9)H), 2.11- 2.29 (1H,m,C(9)H), 2.39-2.51(1H,m,C(8)H), 2.62-2.72(1H,m,C(8)H), 3.64(1H,td,J=11.5,3.5Hz,C(10)Hax), 3.81(1H,dd,J=9.5,5Hz,C(5)H), 3.97(1H,d,J=5Hz,C(6)H), 4.04-4.14(1H,m,C(10)Heq), 4.17(1H,d,J=2.5Hz,C(3)H), 4.40(1H,d,J=3.5Hz,C(2)H), 4.41 (1H,dd,J=9.5,2.5Hz, C(4)H), 5.90(1H,d,J=3.5Hz,C(1)H), 7.19-7.28(3H,m,-S$\underline{Ph}$), 7.52-7.58(2H,m,-S$\underline{Ph}$); *m/z* 494(M^+,10%), 479(M^+- CH_3,3.5), 437(M^+- *t*Bu,1.5), 395(M^+- $C_5H_7O_2$,11.5), 337(40).

(iii) The third component, a colourless oil, was a mixture of (**98a**) and (**98b**), with (**98a**) predominant (192mg, 41%).

(2R,3R)-2,3-O-*Isopropylideneperhydrofuro*[3,2-b]*pyrano*[2,3-e]*pyran*-4a-*ol* (100)

A mixture of sulphide (**98a**) (88.3mg, 0.18mmol) and freshly prepared W-2-

Raney nickel[58] in absolute ethanol (2ml) were stirred vigorously for 0.5h at room temperature. The catalyst was then removed by filtration through celite. Evaporation followed by chromatography on silica furnished a clear colourless oil (28mg, 40%), R_f 0.5(ethyl acetate: petrol, 3:7). This suspected 5-*tetrahydropyranone xylofuranose* (99) was not characterised but was dissolved in tetrahydrofuran (2ml). To the resulting stirred solution at -23°C was added tetra-*n*-butylammonium fluoride (0.08ml, 1M in tetrahydrofuran, 0.08mmol). After stirring at -23°C for 5min the reaction was quenched with saturated aqueous ammonium chloride (2ml) before extracting with dichloromethane (4x5ml), drying over Na_2SO_4 and column chromatography on silica to give the *furo-pyrano-pyranol* (100) as a colourless solid (18.5mg, 94%). Recrystallisation from a diethyl ether/petrol mixture gave rhombohedral crystals m.p. 146-148°C; R_f 0.2(ethyl acetate: petrol, 1:1); (Found: M^+, 272.1254. $C_{13}H_{20}O_6$ requires M,272.1254); $\nu_{max}(CHCl_3)$ 3380(OH), 2925, 2840, 1375, 1150, 1120, 1070, 1000, 965, 890 cm^{-1}; δ(270MHz,$CDCl_3$) 1.33(3H,s, $C\underline{H}_3$), 1.49(3H,s,$C\underline{H}_3$), 1.45-1.94(4H,m,C(8)Hs,C(9)Hs), 2.12-2.32(2H,m,C(5)Hs), 3.23-3.33(2H,m,C(6)H,C(10)Hax), 3.98-4.03(1H,m,C(10)Heq), 4.20(1H,quin, J=2.5Hz,C(4)H), 4.31(1H,d,J=2.5Hz,C(3)H), 4.57(1H,d,J=4Hz,C(2)H), 5.98(1H,d, J=4Hz,C(1)H); *m/z* 272(M^+,2.5%), 257(M^+- CH_3,43), 197(M^+- $C_3H_7O_2$,47).

(2R,3R)-2,3-*Isopropylideneperhydrofuro*[3,2-b]*pyrano*[2,3-e]*pyran*-4a-*ol* (89)

A mixture of sulphide (98b) (39.3mg, 0.08mmol) and freshly prepared W-2-Raney nickel[58] in absolute ethanol (2ml) were stirred vigorously for 15min, at room temperature, after which time the catalyst was removed by filtration through celite. Evaporation furnished a clear colourless oil which was dissolved in tetrahydrofuran (0.8ml) and cooled to 0°C before tetra-*n*-butylammonium fluoride (0.1ml, 1M in tetrahydrofuran, 0.1mmol) was added with stirring. After stirring at 0°C for 5min the reaction was quenched with saturated aqueous ammonium

chloride (2ml) before extracting with dichloromethane (4x5ml), drying over Na_2SO_4 and column chromatography on silica to give the furo-pyrano-pyranol (89) as a viscous colourless oil (6mg, 25%), R_f 0.3(ethyl acetate: petrol, 1:1), which showed spectral data identical with those obtained from the product of reduction of the thiocarbonyl imidazole derivative (88).

Attempted preparation of 3-(O-*Benzyl*)-5-*deoxy*-1,2-O-*isopropylidene*-5-(3-*oxotetrahydropyran*-2-*yl*)-5-*phenylthio*-α-D-*xylose* (80)

To a stirred solution of the crude α-chlorosulphide (79) (88.8mg, 0.22mmol) and silyl enol ether (9) (41.1mg, 0.19mmol) in dichloromethane (0.5ml) at -23°C, under nitrogen, was added titanium tetrachloride (0.2ml, 1M in dichloromethane, 0.2 mmol). After 15min reaction was quenched by rapidly injecting saturated aqueous sodium bicarbonate (0.5ml). The resulting emulsion was allowed to warm to room temperature before extracting with dichloromethane (4x5ml), drying over Na_2SO_4 and evaporation to give an oil which was purified by column chromatography on silica. The major product isolated was the 5-*phenylthio*-α-D-*xylose* (101) as a colourless solid (37mg, 65%). Recrystallisation from an ethyl acetate/petrol mixture gave rhombohedral crystals, m.p. 102-103°C; R_f 0.46(ethyl acetate: petrol, 1:1); (Found: C,59.60;H,6.47. $C_{14}H_{18}O_4S$ requires C,59.55;H,6.42%); ν_{max}(nujol mull) 3400(OH), 2890, 2830, 1575, 1445, 1370, 1210, 1155, 1060, 995, 850, 730 cm^{-1}; δ(270MHz,$CDCl_3$) 1.29(3H,s,$C\underline{H}_3$), 1.43(3H,s,$C\underline{H}_3$), 1.94(1H,brs,O$\underline{H}$), 3.16(1H,dd,J=13.5,9Hz,C(5)H), 3.29(1H,dd, 13.5,5Hz,C(5)H), 4.23-4.33(2H,m,C(3)H,C(4)H), 4.51(1H,d,J=3.5Hz,C(2)H), 5.91(1H,d,J=3.5Hz,C(1)H), 7.19-7.45(5H,m,-S$\underline{Ph}$); *m/z* 282(M^+,66%), 267(M^+-CH_3,10), 207(10), 159(M^+-C_7H_7S,52), 123(M^+-$C_7H_{11}O_4$,34).

5-Deoxy-1,2-O-isopropylidene-5-phenylthio-α-D-xylofuranose (101)

To a stirred solution of the crude α-chlorosulphide (79) (215mg, 0.53mmol) in dichloromethane (2ml) at -23°C, under nitrogen, was added titanium tetrachloride (0.53ml, 1M in dichloromethane, 0.53mmol). After 15min, stirring at -23°C, reaction was quenched by rapidly injecting saturated aqueous sodium bicarbonate (1ml). The resulting emulsion was allowed to warm to room temperature before extracting with dichloromethane (4x2ml), drying over Na_2SO_4 and evaporation to give a clear yellow oil.

To a solution of the above yellow oil in methanol (2ml) was added a solution of 2,4-dinitrophenylhydrazine (250mg, 1.3mmol) and conc sulphuric acid (0.4ml) in methanol (5ml). After 15min an orange precipitate formed which was collected by filtration and recrystallised from ethyl acetate to give benzaldehyde 2,4-dinitrophenylhydrazone (50mg, 35%) as orange needles, m.p. 239-242°C, mixed m.p. 241-242°C, with authentic material (lit.[61], m.p. 237°C).

Following filtration, the mother liquors were neutralised with saturated aqueous sodium bicarbonate and extracted with dichloromethane (4x10ml). Drying (Na_2SO_4) was followed by evaporation and column chromatography on silica to give a colourless solid (97mg, 65%). Recrystallisation from an ethyl acetate/petrol mixture gave the 5-phenylthio-α-D-xylofuranose (101) as rhombohedral crystals, m.p. 101-103°C, which showed data identical with those of the compound synthesized in the previous experiment.

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CHAPTERS 2 AND 3

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LITHIATED DIHYDROPYRANS AS KETONE ENOLATE EQUIVALENTS: A MODEL STUDY FOR THE HERBICIDINS

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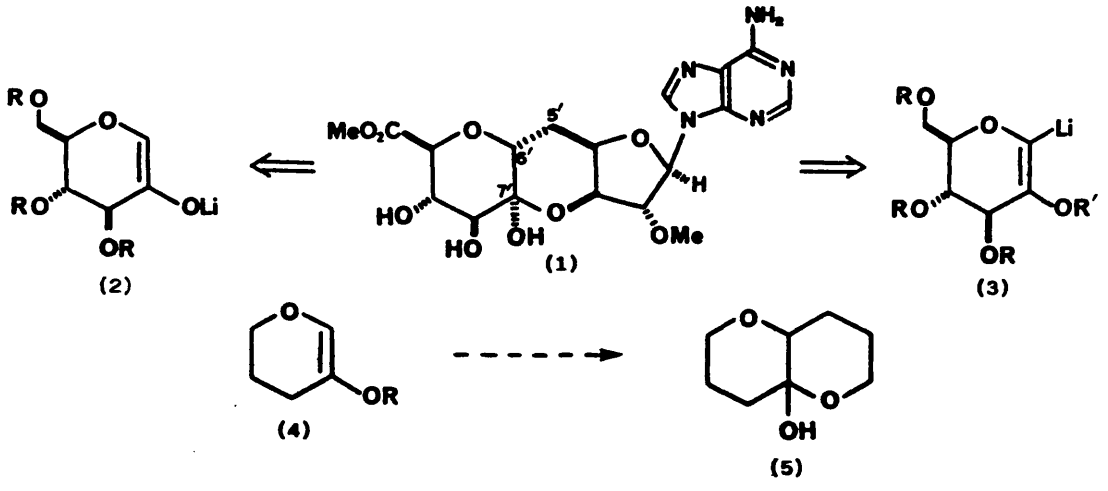
Summary: The synthesis of 6-lithio-5-methoxy-3,4-dihydro-2H-pyran (6) and its use as a regiospecific ketone enolate equivalent is described for the first time. This anion has been used to prepare the bicyclic hemiketal (5), a synthetic model for herbicidin B (1).

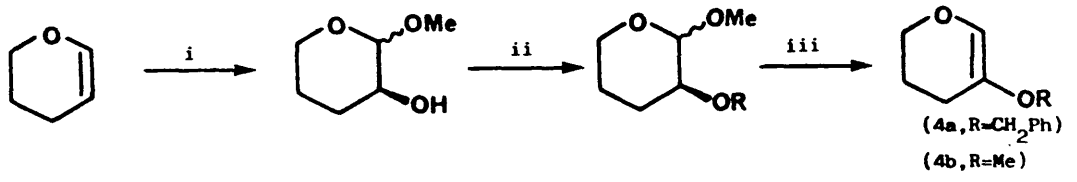
The herbicidins, illustrated below by herbicidin B (1), are a structurally unusual group of tricyclic nucleosides containing both a C-glycoside linkage (C-5 - C-6) and an adjacent hemiketal function (C-7).[1]

Any synthetic effort in this area must take account of the relationship between these two structural features, with the carbohydrate-derived enolate (2) emerging as a logical precursor. However access to this enolate, by deprotonation of the corresponding ketone, is not a trivial matter since in related systems (including carbohydrate-derived ketones) the observed mode of enolization is away, rather than towards, the conformationally constrained ring oxygen atom.[2]



β-Lithiated enol ethers have previously been used as enolate equivalents[3] and an alkenyl anion such as (3) could therefore function as a synthetic eqivalent of the regiospecific enolate (2)[4]. With this strategy in mind we have undertaken a model study, the synthesis of the bicyclic hemiketal (5), which is based on the lithiation of a 5-alkoxy-3,4-dihydro-2H-pyran (4).[5]

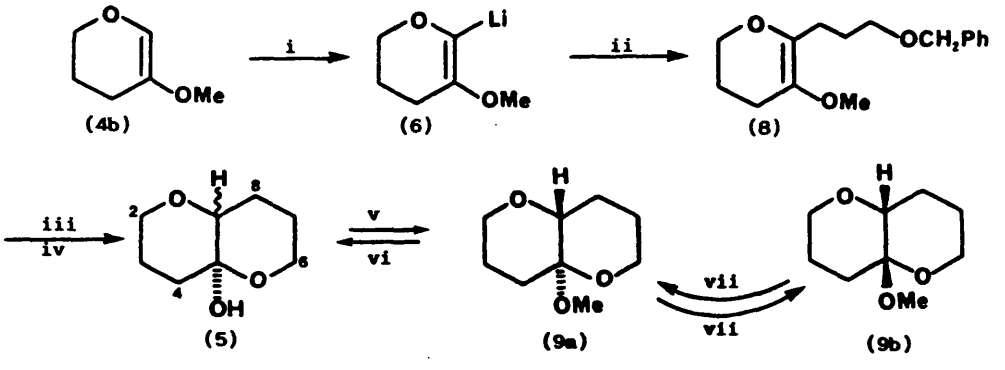
The required alkoxydihydropyrans (4a, R = CH_2Ph) and (4b, R = Me) were available in a four step sequence, starting from dihydropyran, as shown in Scheme 1.



SCHEME 1. Reagents:i,mCPBA,MeOH(85%);ii,NaH,DME,$PhCH_2Br$(95%) or MeI(98%); iii,H_3O^+,then $MeSO_2Cl$,NEt_3(R=CH_2Ph,47%; R=Me,48%).

Metallation [Bu^tLi, THF, -78°C] of (4a) proceeded smoothly. However addition of allyl bromide to the resulting anion led only to the product derived from benzylic deprotonation. No evidence for the formation of an alkenyl anion was observed.

This complication does not arise with the methoxy derivative (4b) which underwent metallation [Bu^nLi, THF, 0°C to 50°C] to give alkenyl lithium (6). Alkylation of this species with the bifunctional electrophile (7, R = CH_2Ph) gave adduct (8) and enol ether cleavage followed by hydrogenolysis of the resulting ketone gave bicyclic hemiketal (5) in 42% overall yield from (4b) (Scheme 2).

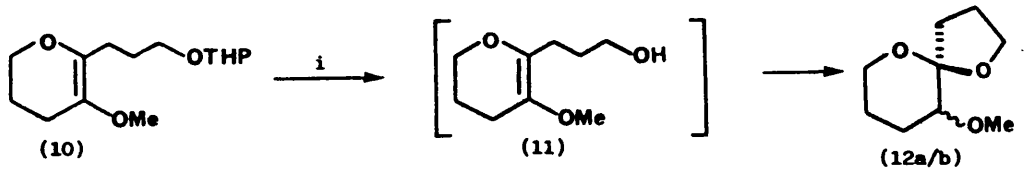


SCHEME 2. Reagents:i,Bu^nLi,THF,0°C to 50°C;ii,I∿∿OR(7,R=CH_2Ph)(65%); iii,Me_3SiCl,NaI,MeCN(70%);iv,H_2,10%Pd on C(93%);v,MeOH,H^+(98%);vi,H^+(98%);vii,MeOH,H^+.

Although the *cis* -configuration of hemiketal was (5) adopted in the crystalline state[6], (ORTEP diagram of *cis*-(5) is shown in Figure 1),^{1}H nmr spectroscopy revealed that, on dissolution, an equilibrium was rapidly established in which *cis*- and *trans* - (5) were present in approximately equal amounts. Methanolysis of (5) gave a 1:1 mixture of the readily separable bicyclic ketals (9a) and (9b); these ketals underwent both equilibration with one another and hydrolysis back to hemiketal (5).[7]

In principle a more direct route to (5) is available if the ketone and primary hydroxyl functions can be released under the same reaction conditions, rather than in a stepwise fashion. Accordingly the THP-protected adduct (10) was prepared, in 54% yield, by reaction of (6) with (7, R = THP). However exposure of (10) to aqueous acid failed to give hemiketal (5), instead a 1:1 mixture of spiroketals (12a) and (12b) were isolated (Scheme 3).[8] Some evidence has been obtained for the intermediacy of alcohol (11) and

clearly protonation of the enol ether and the subsequent mode of cyclisation is being controlled by the ring oxygen atom. Attempts were made to interconvert the fused and spiro bicyclic ketals [(9a/b) ⇌ (12a/b)] but, even under forcing conditions, these failed.



SCHEME 3. Reagents: i, H_3O^+ [1:1 mixture of(12a/12b)(60%)]

In summary, lithiation of (4b) provides alkenyl anion (6), a convenient synthetic equivalent of the regiospecific enolate (13). The bicyclic hemiketal (5) has been prepared in a straightforward manner but the choice of protecting groups is crucial to the success of this sequence.

We are currently extending the application of this methodology to encompass the more complex alkoxyglucal (3),[9] with a synthesis of herbicidin B as our objective.

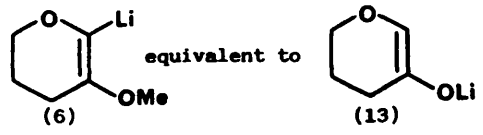
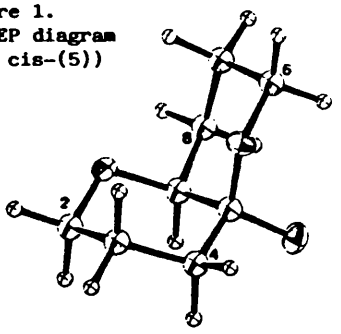


Figure 1. (ORTEP diagram of cis-(5))



Acknowledgement: We thank SERC and the Wellcome Laboratories for a CASE award and Drs O Howarth (Warwick) D W Brown (Bath) and M Seddon (Wellcome) for help with nmr spectra.

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4. 2-Deoxy-C-glycosides have recently been prepared using 1-lithio-3,4,6-trisubstituted glycals.

a) P. Lesimple, J.-M. Beau, and P. Sinäy, J. Chem. Soc., Chem. Commun., 1985, 894;

b) K.C. Nicolaou, C.-K. Hwang, and M.E. Duggan, J. Chem. Soc.,Chem. Commun., 1986, 925;

c) S. Hanessian, M. Martin and R.C. Desai, J. Chem. Soc., Chem. Commun., 1986, 926;

d) P. Lesimple, J.-M. Beau, G. Jaurand, and P. Sinäy, Tetrahedron Letters, 27, 6201, (1986).

5. The only other reported example of this type of dihydropyran,(4, R = $SiMe_3$), is formed as the minor component by silylation of the enolate derived from 2H-dihydropyran-3(4H)one.[2a] For anions related to (6) see (a) lithiation of 1,4-dioxene: R.W. Saylor and J.F. Sebastian, Synth. Commun., 12, 579, (1982) and M. Fetizon, I. Hanna and J. Rens, Tetrahedron Letters, 26, 3453, (1985); b) lithiation of 1,2-dimethoxyethene: C.N. Skold, Synth. Commun.,6, 119, (1976).

6. Hemiketal (5) crystallised (ether-hexane) in space group $P2_1/n$ with a = 6.042(2), b = 18.102(2), C = 7.537(2) Å and β = 103.18(2)° and Dcalcd = 1.309gcm^{-3} for Z = 4 at room temperature. The structure was solved by direct methods using 597 unique reflections with I > 3σ I and refined by full-matrix least squares to final residuals of R = 6.9 and R_w = 6.75.
The ORTEP diagram of *cis*-(5) is shown in Figure 1.

7. All new compounds have been fully characterised.
(9a) δ($CDCl_3$, 400 MHz), 3.98 (1H, ddt, J11, 5, 1.5 Hz, $H2_{eq}$), 3.62 (1H, ddd, J12, 11,3Hz $H6_{ax}$), 3.54 - 3.44 (2H, m, $H2_{ax/6eq}$), 3.23 (3H, s, OMe), 3.22 (1H, dd, J11.5, 4Hz, $H8a_{ax}$), 2.12 (1H, m, $H4_{eq}$), 1.90 - 1.62 (5H, m, $H8_{ax/eq}$, $H7_{ax/eq}$, $H3_{ax}$), 1.53 (1H, m, $H3_{eq}$), 1.37 (1H, td, J14, 4Hz, $H4_{ax}$).
(9b) δ($CDCl_3$, 400 MHz), 3.96 (1H, ddt, J11, 4.5, 2Hz, $H2_{eq}$), 3.72 - 3.61 (2H, m, $H6_{ax/eq}$) 3.37 (1H, ddd, J13, 11, 2Hz, $H2_{ax}$), 3.22 (1H, t, J2.5Hz, $H8_a$), 3.21 (3H, s, OMe), 2.10 (1H, m, $H4_{eq}$), 2.02 (1H, m, $H8_{ax}$), 2.00 - 1.80 (2H, m, $H7_{ax}$, $H3_{ax}$), 1.65 (1H, m, $H8_{eq}$), 1.38 (1H, td, J13, 5Hz, $H4_{ax}$), 1.24 (1H, m, $H7_{eq}$).

8. The fully coupled ^{13}C nmr spectrum was particularly useful in assigning the structures of (12a/b). In both cases the methoxy group was observed as a quartet of doublets ($^1J_{C-H}$ = 151 Hz and $^3J_{C-H}$ = 5.5 Hz). Although (12a) and (12b) have been separated we have been unable to assign the relative configurations of these ketals. In addition, (12a) and (12b) undergo facile acid-catalysed interconversion.

9. The metallation of carbohydrates closely related to (2) has been reported very recently. R.R. Schmidt, R. Preuss, and R. Betz, Tetrahedron Letters, 28, 6591, (1987).

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TETRAHEDRON LETTERS, VOL. 30, 1989 (*In press*)

REGIOSPECIFIC TETRAHYDROPYRAN-3-ONE ENOLATES. SYNTHESIS AND REACTIVITY OF SILYL ENOL ETHER DERIVATIVES.

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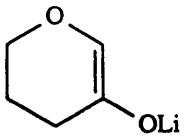
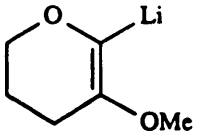
Summary. The synthesis and reactivity of the silyl enol ether (3) is reported. This reagent complements the reactivity of the lithiated enol ether (2) previously used as a synthetic equivalent of the regiospecific tetrahydropyran-3-one enolate (1).

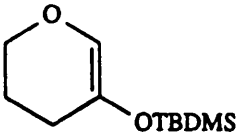
As part of a general study relating to the synthesis of complex tetrahydropyrans, we recently reported that the β-alkoxy alkenyl lithium (2) can be used as an effective equivalent of the regiospecific enolate (1,R=H).[1] This enolate regioisomer is difficult to obtain in useful yields from the corresponding ketone since the preferred mode of enolization of pyran-3-ones tends to be away rather than towards the ring constrained heteroatom.[2] In a more conventional sense, the introduction of silyl enol ethers greatly expanded the synthetic scope of enolate chemistry by providing a means of introducing an electrophile to a ketone under nonequilibrating conditions.[3] Not only do these labile silyl derivatives provide access to the corresponding enolate, but they are also compatible with a range of "S_N1-type" electrophiles in the presence of Lewis acids.[4]



(1)



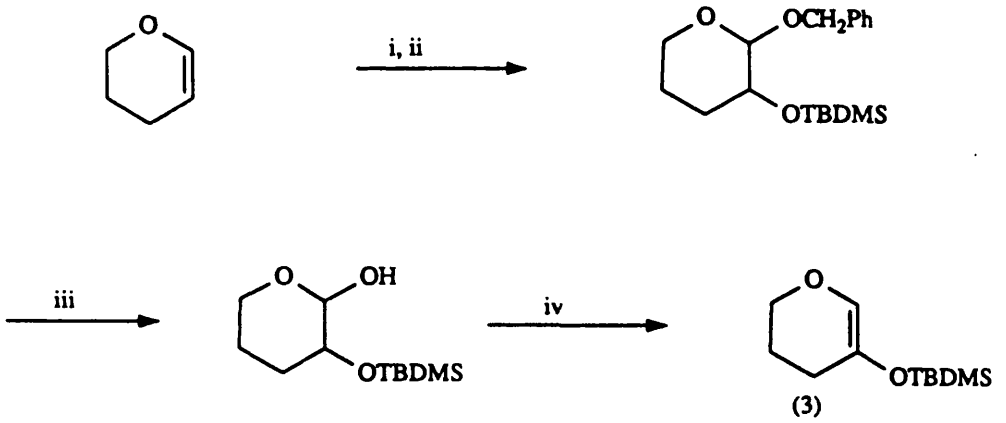
(2)



(3)

A silyl derivative of enolate (1) would be anticipated to provide significant advantages over the alkenyl lithium (2), the scope of which is limited by the highly basic nature of this species. In this paper we describe the synthesis and reactivity of the t-butyldimethylsilyl(TBDMS) enol ether derivative (3).

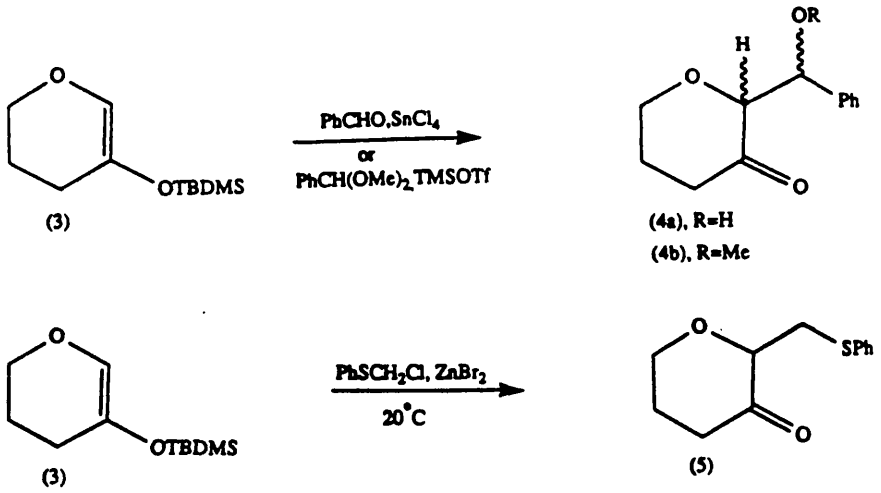
The synthesis of (3) is shown in Scheme 1. The only significant difference between this route and that used to prepare the methoxy precursor of (2)[1] was the use of benzyl alcohol rather than methanol in the peracid oxidation of dihydropyran.



SCHEME 1. Reagents: i, m-CPBA, $PhCH_2OH$ (58%); ii,TDBMSCl,DBU (94%); iii,H_2 Pd/C (86%); iv,$MeSO_2Cl$, Et_3N (80%).

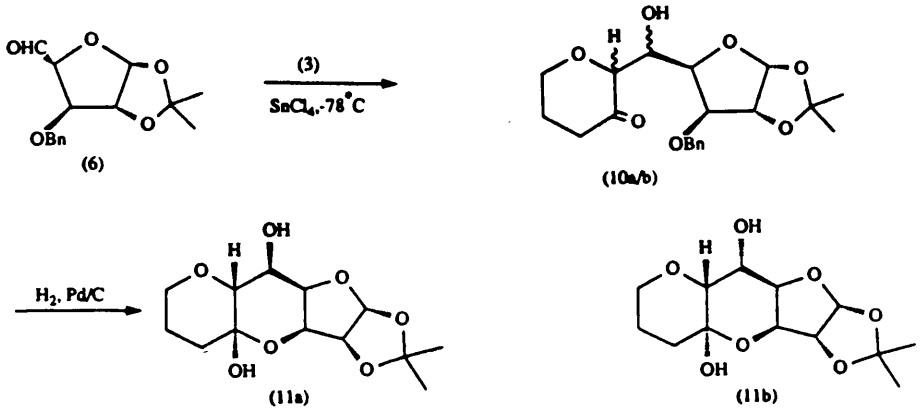
In this way the corresponding hemiacetal was obtained by hydrogenolysis rather than by acid-catalysed hydrolysis which led to extensive migration and loss of the silyl moiety.

Reaction of benzaldehyde with silyl enol ether (3) under Mukaiyama's conditions[5] ($SnCl_4$,CH_2Cl_2,-78°C) was unselective, giving the aldol product (4a) in 50% yield as a 3:2 mixture of *syn* and *anti* diastereoisomers. The condensation of (3) with benzaldehyde dimethyl acetal in the presence of trimethylsilyl trifluoromethanesulphonate[6] was also examined. Under these conditions a higher level of selectivity was observed with (4b) being isolated as a 5:1 mixture of isomers.[7] Phenylthiomethylation[8] of (3) was achieved using α-chloromethylphenylsulphide in the presence of $ZnBr_2$ in CH_2Cl_2 at 20°C to give (5) in 64% yield.



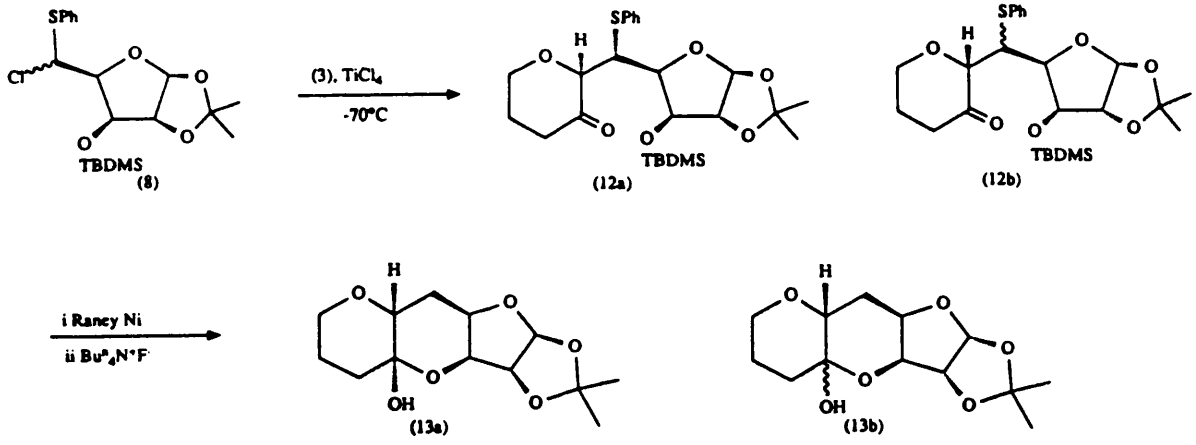
Because of their relevance to the synthesis of the herbicidin class of tricyclic nucleosides, we have also studied the reactivity of silyl enol ether (3) towards the more complex carbohydrate-derived electrophiles, aldehyde (6)[9] and α-chlorosulphide (7)[10]

Condensation of (6) with (3), using $SnCl_4$ as the Lewis acid of choice, in CH_2Cl_2 at -78°C gave a 1:1 mixture of two inseparable diasteroisomeric aldol adducts (**10a**) and (**10b**) in 35% yield. Hydrogenolysis of this mixture gave a separable mixture of the tetracyclic hemiketals (**11a**) and (**11b**) in 50% yield. The structural assignments of (**11a/b**) are based on extensive ^{1}Hnmr studies.



In the presence of $TiCl_4$ (CH_2Cl_2,-70°C), α-chlorosulphide (**8**) reacted with (**3**) to give a 4:1 mixture of two diasteroisomers in a combined yield of 70%. The major component (**12a**) was readily separated and the structure of this adduct was established by x-ray crystallographic analysis.[11]

Raney nickel desulphurization of (**12a**) followed by fluoride ion-induced desilylation gave hemiketal (**13a**) in 50% overall yield. This structural assignment was also confirmed by x-ray crystallography.[12] In a similar fashion the other adduct (**12b**) was converted to hemiketal (**13b**), but the stereochemical assignment of the anomeric hydroxyl of this isomer has not been established unambiguously.



In summary, the silyl enol ether (**3**) complements the reactivity of the alkenyl lithium (**2**), but the chemistry described above is likely to be applied more readily to the synthesis of more complex tetrahydropyran-3-ones.

Acknowledgements. We wish to thank the Wellcome Research Laboratories and SERC for provision of a CASE award to Paul Cox and Dr O Howarth (Warwick University) for advice concerning ^1H nmr assignments.

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7. The *syn/anti* assignment of adducts (**4a**) and is based on the magnitude of the coupling constant to the benzylic methine proton ($^3J_{syn}$=3.5Hz, $^3J_{anti}$=7.5Hz). Structural assignments adducts for (**4b**) have not been made as yet.
8. For a comprehensive discussion of the Lewis acid-promoted phenylthioalkylation of silyl enol ethers see I. Paterson, *Tetrahedron*, **1988**, *44*, 4207.
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10. Chlorosulphide (**7**) was prepared in three steps (60% overall yield) from 1,2-O-isopropylidene-5-toluene-p-sulphonyl-α-D-xylofuranose, (R.C. Young, P.N. Kent and R.A. Dwek, *Tetrahedron*, **1970**, *26*, 3983) by (i) silylation (TBDMSCl,DBU); ii, PhSH, DBU; iii,N-chlorosuccinimide.
11. Chlorosulphide adduct (**12a**) crystallised (hexane) in space group $P2_12_12_1$ with a=12.071(3), b=12.134(7), c=38.748(10)Å and Dcalcd=1.158gcm^{-3} for Z=8 at room temperature. The asymmetric unit consisted of two discreet molecules of (**12a**), which were identical to each other within experimental error. The structure was solved by direct methods using 1765 reflections with I≥3σI and refined by blocked matrix least squares, where each molecule of (**12a**) was treated separately, to final residuals of R=9.2% and R_w=8.39%.
12. Hemiketal (**13a**) crystallised (hexane/ether) in space group $P2_12_12_1$ with a=8.086(2), b=18.193(4), c=9.612(3)Å and Dcalcd=1.306gcm^{-3} for Z=4 at room temperature. The structure was solved by direct methods using 684 reflections with I≥3σI and refined by full matrix least squares to final residuals of R=9.94% and R_w=10.50%.

APPENDIX

X-RAY CRYSTAL DATA

1. Hemiketal (29) (Figure 2) crystallised (ether-hexane) in space group $P2_1/n$ with a=6.042(2), b=18.102(2), c=7.537(2)Å and β=103.18(2)° and Dcalcd=1.309gcm^{-3} for Z=4 at room temperature. The structure was solved by direct methods using 597 unique reflections with I>3σI and refined by full-matrix least squares to final residuals of R=6.9% and R_w=6.75%.

2. Sulphide (98a) (figure 6) crystallised (hexane) in space group $P2_12_12_1$ with a=12.071(3), b=12.134(7), c=38.748(10)Å and Dcalcd=1.158gcm^{-3} for Z=8 at room temperature. The asymmetric unit consisted of two discreet molecules of (98a), which were identical to each other within experimental error. The structure was solved by direct methods using 1765 reflections with I≥3σI and refined by blocked matrix least squares, where each molecule of (98a) was treated separately, to final residuals of R=9.2% and R_w=8.39%.

3. Furo-pyrano-pyran (100) (Figure 7) crystallised (hexane/ether) in space group $P2_12_12_1$ with a=8.086(2), b=18.193(4), c=9.612(3)Å and Dcalcd=1.306gcm^{-3} for Z=4 at room temperature. The structure was solved by direct methods using 684 reflections with I≥3σI and refined by full matrix least squares to final residuals of R=9.94% and R_w=10.50%.

Atomic co-ordinates, bond lengths and angles and thermal parameters will be deposited at the Cambridge Crystallographic Data Centre.

(Compound numbers refer to results and discussion section).